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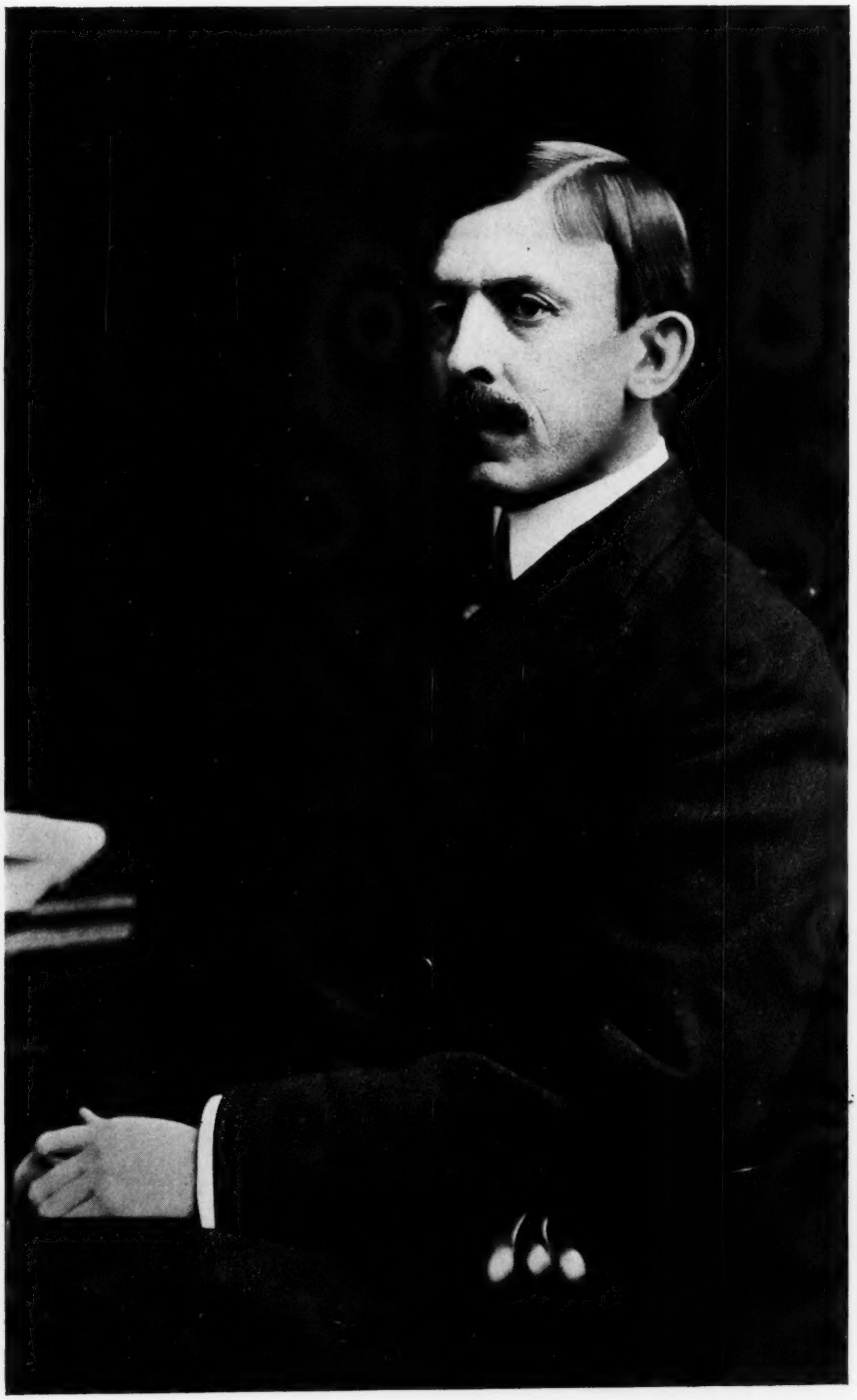

Hermann M. Biggs

Hermann M. Biggs

1859-1923

Hermann Michael Biggs was born at Trumansburg, New York, September 29, 1859, and died in New York City June 28, 1923, leaving a widow and two children, a son and a daughter. His family was of Anglo-Saxon stock and had been in this country since the seventeenth century. After attending preparatory schools at Trumansburg and Ithaca, he worked in a general store until his twentieth year, when he entered the freshman class at Cornell. During the next few years he developed a most remarkable power of concentration and application, which lasted throughout life. So assiduous was he in his work that he received the degree of A.B. from Cornell in 1882 and the degree of M.D. in 1883, graduating first in his class at the Bellevue Hospital Medical College, although he attended the medical school only two years, the first year while he was still a student at Cornell.

After an interneship at Bellevue Hospital Dr. Biggs studied at Greifswald with Professor Loeffler, and then in Berlin in Robert Koch's laboratory. Association with Koch aroused his intense interest in the entire problem of tuberculosis, and upon his return to New York in 1885 he found that he was the only physician in the city who was able to stain the tubercle bacillus, an acquisition which he found ample opportunity to demonstrate at Bellevue Hospital. He continued his laboratory work as director of the Carnegie Laboratory, where he gave the first instruction on bacteriology in the United States, and was instrumental in preparing the plans and securing an appropriation for the creation of the first municipal diagnostic laboratory in the world. He continued his association with the Bellevue Hospital Medical College and was closely connected with it from 1886 until 1915, successively as lecturer on pathology, demonstrator of anatomy, professor of pathology, professor of materia medica and therapeutics, adjunct professor of the principles and practice of medicine and, from 1912, professor of the practice of medicine. He was for many years engaged in hospital work, having been visiting physician to the Almshouse Hospital, visiting physician at Bellevue and St. Vincent's and, from 1886 until his death, he was closely associated with Bellevue Hospital.

Early in his career Dr. Biggs fully realized the possibilities of preventive medicine, as had already been shown by his interest in developing the first municipal diagnostic laboratory. His work in preventing the entrance of cholera into New York City in 1892 was most effective. From that date he was for twenty-three years closely connected with the New York City Health Department as director of the laboratory. In 1902 Mayor Low asked him to become Commissioner of Health. After a number of conferences with the Mayor, he was appointed General Medical Officer, a position that he held from 1902 to 1914.

Dr. Biggs is best known for the important advances which he made in the application of scientific knowledge in official health work, his organization of the New York City laboratory, the introduction and manufacture of diphtheria antitoxin for which he was responsible in 1895, his effective handling of a severe typhus epidemic in New York City in 1897 and his method of examining steerage passengers from cholera ports, which established a routine procedure now generally used in times of epidemic. His most notable contribution to preventive medicine was his continued and finally successful efforts to secure the proper system for the compulsory reporting of deaths and cases of tuberculosis, for the isolation of tuberculous patients in special institutions, for municipal ordinances for the prevention of promiscuous spitting, for the development of a great municipal sanatorium and for the drafting and securing the passage of many far reaching legislative measures which have been continuously in use for the prevention of tuberculosis in New York City and State.

In 1912 Dr. Biggs was appointed by the Governor of New York chairman of a committee to prepare a draft for a new public health law. The legislation recommended by this committee was passed by the legislature at the end of the 1913 session, and in many parts of the country the New York State public health law has since been looked up to as a model health law for a state. In 1914 Dr. Biggs was appointed State Commissioner of Health by Governor Glynn and chairman of the State Public Health Council, both of which positions he held until his death. As in his work in New York City, he was particularly interested in the scientific aspects of the work of the State Department of Health, and with painstaking care he selected a director of the laboratory, Dr. Augustus B. Wadsworth, who he knew could realize his dream of establishing a splendid diagnostic laboratory which would also be a centre of scientific research. In this laboratory Dr. Biggs constantly suggested the study

and possible application of new methods for diagnosis and new laboratory projects which might be applicable in the prevention of disease. Throughout life he was always imbued with a scientific spirit and a desire to know all the facts and, when these were known, to apply such measures as were necessary to assist in the eradication of any disease.

Dr. Biggs was a member of many medical societies, to which he frequently gave his time and counsel, and was often recognized by them by being elected president. He was an active member of the New York City Tuberculosis Committee of the Charity Organization Society from its inception and, later, when this society became the New York Tuberculosis Association. He was also a member of the New York State Tuberculosis Committee of the State Charities Aid Association. He was a member and twice President of the National Association for the Study and Prevention of Tuberculosis (now the National Tuberculosis Association), and at the time of his death he was President of the American Social Hygiene Association. His counsel was valued at the Rockefeller Institute, of which he was a Scientific Director since its organization, and he was a member of the International Health Board of the Rockefeller Foundation. He held honorary degrees from New York, Rochester and Harvard Universities.

One might assume that, with all the activities in which Dr. Biggs was engaged, he would have had no time to earn a living; but such was the nature of the man that he was able to build up a large practice and during the last fifteen years he was engaged in a great deal of consulting work which frequently called him to distant points. His patients placed their entire confidence in him and among them were the very rich, the very poor and those from all walks of life. In his practice he was remarkably successful in diagnosis and skilled in treatment, and took infinite pains to see that each patient received the best of care. Those who knew him best or were associated with him in any of his activities soon learned to appreciate and admire that rare quality previously referred to, and to which he some times alluded impersonally, saying, "It is a curious fact that when four or five men discuss a problem in a committee for several hours and meet again several days later, no one gives any thought to the matter until the committee reconvenes. It is really very simple just to think a few minutes at odd moments and, when you return to the committee meeting, you have the solution of the problem and find that the other members assent and say, 'That's exactly what I thought.' You

know most people don't think or, if they do think, they don't think things through."

Dr. Biggs was widely known in medical and health circles but he never sought notoriety, was always loath to speak at a public meeting or even in small groups, but when he did his remarks were always instructive, clearly stated and most convincing. His knowledge of public health work and administration was perhaps no greater than that of many other men, but he was far above any other man in public health administration in the United States by reason of the ability to judge accurately the relative value of public health procedures and a political instinct to know in advance when it would be possible to secure the adoption of a new law or municipal ordinance and also to realize when public opinion would support a new measure.

This rare judgment, together with a very vivid imagination, made him the great leader who first instituted and carried out many of the public health procedures now in common use. For many years, and even to-day, various communities have not been able to enact many of these health reforms inaugurated by Dr. Biggs. At the meeting of the International Congress on Tuberculosis in London in 1901 foreign delegates marvelled when they heard Dr. Biggs's report on what had been accomplished in the city of New York for the prevention of tuberculosis.

No one associated with Dr. Biggs could have failed to admire his marvellous comprehension and unusual judgment, his enormous capacity for work and his ability to crowd into a short hour what many would devote a day to. By nature modest and unassuming, shy and retiring, he did not always make friends readily, but those to whom he gave of himself warmly appreciated his sincerity, loyalty and companionship. It was a rare privilege to have known a man who was truly great.

L. R. W.

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1885

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1886

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1894

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1921

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1922

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TUBERCULOSIS OF THE INTESTINES[1]

H. SCHWATT
in collaboration with
M. M. STEINBACH

It has become commonplace that tuberculous ulceration of the intestines is much more frequently recognized at autopsy than during life, because, in the majority of cases, of a complete absence of symptoms, irrespective of the extent, severity or location of the involvement.

For the purpose of further inquiry into the symptomatology and diagnosis of this complication of chronic phthisis we have studied the pathological findings in 199 consecutive autopsies from the Tuberculosis Division of Montefiore Hospital and the clinical course in these cases.

The frequency with which tuberculous ulceration of the intestines has been observed in fatal phthisis varies considerably. Fenwick and Dodwell (1) found ulceration in 56.6 per cent of 883, Eisenhardt (2) in 56.7 per cent of 1000, Walsh (3) in 76 per cent of 100, Zahn (4) in 63.2 per cent of 1528 and Engelsmann (5) in 92.6 per cent of 108 autopsies. In our 199 cases ulceration was present in 130 or 65.3 per cent. Four cases showed tubercles without ulceration.

Autopsy reports probably do not always represent the true incidence of tuberculous disease of the intestines. Even if the autopsies are carefully performed very small lesions may be easily overlooked. At any rate, there is no doubt that, with laryngeal tuberculosis, it is one of the two most frequent complications of chronic ulcerative pulmonary tuberculosis.

I: PATHOLOGICAL OBSERVATIONS

1. Distribution of Ulcers

The symptomatology of tuberculous ulceration of the intestines is so frequently correlated in the literature with the site of the lesions that it is important to study their distribution and the comparative frequency with which certain segments of the tract are involved (tables 1 and 2).

[1] From the Montefiore Hospital for Chronic Diseases and Bedford Hills Sanatorium, New York.

TABLE 1

Distribution of lesions

	NUMBER OF CASES WITH	
	Ulcers and tubercles	Ulcers
Duodenum, jejunum, ileum	1	1
Duodenum, jejunum, ileum, cecum, colon	1	1
Duodenum, jejunum, ileum, appendix, colon	1	1
Jejunum	1	1
Jejunum, appendix, colon, rectum	1	1
Jejunum, ileum	5	6
Jejunum, ileum, cecum	5	3
Jejunum, ileum, cecum, appendix	1	1
Jejunum, ileum, cecum, appendix, colon	14	12
Jejunum, ileum, cecum, colon	8	8
Jejunum, ileum, cecum, colon, rectum	1	1
Jejunum, ileum, cecum, appendix, colon, rectum	6	6
Jejunum, ileum, colon	1	1
Ileum	22	20
Ileum, cecum	12	14
Ileum, appendix	1	1
Ileum, appendix, colon	1	0
Ileum, cecum, appendix	5	4
Ileum, cecum, appendix, colon	6	6
Ileum, cecum, appendix, colon, rectum	2	2
Ileum, cecum, colon	10	11
Ileum, cecum, rectum	1	1
Ileum, colon	4	5
Cecum	6	5
Cecum, appendix	1	1
Cecum, appendix, colon	2	2
Cecum, appendix, colon, rectum	1	1
Cecum, colon	3	3
Cecum, colon, rectum	1	1
Appendix	2	2
Colon (sigmoid)	1	1
Rectum	2	2
Small intestine	2	2
Small and large intestine	1	1
Intestine	2	2
	134	130

In our cases the small intestine (109 times) was involved somewhat more frequently than the large intestine (98 times). The small intestine alone was the seat of disease 30 times and the large intestine alone 19 times. The small and the large intestines were ulcerated in 80 or 62.5 per

cent. In over 75 per cent the lesions involved more than one subdivision of the tract (table 3).

Duodenal ulcers occurred in 3 cases, with involvement once of the small intestine alone and twice of the small and large intestines. The following cases showed an interesting distribution of the lesions from the standpoint of the earliest site of the disease.

TABLE 2

Relative frequency of ulceration in the different segments of the intestine

	TIMES	PER CENT	SOLE SEAT OF DISEASE	
			Times	Per cent
(128 cases)				
Small intestine	109	85.2	30	23.4
Large intestine	98	76.2	19	15.0
(125 cases)				
Duodenum	3	2.4		
Jejunum	43	34.4	1	08.0
Ileum	105	84.0	20	16.0
Cecum	84	67.2	5	04.0
Appendix	40	32.0	2	01.6
Colon	63	50.4		
Sigmoid			1	08.0
Rectum	15	12.0	2	01.6

TABLE 3

Showing comparative frequency of number of segments with ulceration

NUMBER OF SEGMENTS	NUMBER OF TIMES	PER CENT
1	31	24.8
2	30	24.0
3	24	19.2
4	17	13.6
5	17	13.6
6	6	4.8

Autopsy 3147: Many advanced ulcers with ragged margins and infiltrated bases from the lower portion of the duodenum to within four feet of the ileocecal valve. The lower ileum and the cecum normal; the appendix with three fairly recent ulcers and the ascending colon with two small recent ulcers.

Autopsy 3576: In the duodenum, immediately distal to the pylorus, an irregular, elevated area about 1.5 cm. in diameter, in the centre of which are two small, ragged ulcers, 2 mm. in diameter. At the junction of the jejunum

and ileum a single recent, hemorrhagic ulcer. Near the ileocecal valve numerous, small, recent ulcers, about 2 mm. in diameter.

Ulceration of the jejunum alone, or of the jejunum and large intestine without involvement of the ileum, is infrequent. There was only one case of each in our series, both of which presented unusual features of distribution of the lesions, as follows:

Autopsy 3441: In the jejunum about ten ulcers: the ileum and cecum negative; the appendix extensively diseased. The ascending colon negative; transverse and descending colon the seat of three large ulcers. One ulcer in the rectum, 3.5 inches above the anus.

Autopsy 3559: One large ulcer, extending to the serosa, in the upper portion of the jejunum 2 feet from the pylorus.

The ileum was the most frequently involved segment of the intestines. It was the seat of ulcers 105 times, or in over 98 per cent of 107 cases in which the small intestine was involved with or without lesions in the large intestine. Ulceration of the ileum without the jejunum (63 times) was more frequent than of ileum with jejunum (42 times).

The ileum was also the most frequent site of sole ulceration. It occurred in 20, or 16 per cent, of 129 cases in which the location of the lesions was noted in detail. In 16 of these the lesions were located in the lower ileum, from a few centimetres to several inches above the ileocecal valve; in one case in the upper and middle portions; in two cases in the middle portion; and in one case in the middle and lower portions. In over 75 per cent there were only one or two small, superficial ulcers, and in a small number from three to five ulcers. In a few cases they were more numerous. Extensive involvement with advanced ulceration occurred in only two cases, one of which presented several perforations in the middle portion. Two cases, which follow, showed tubercles only:

Autopsy 3170: One pinhead-sized yellow opaque tubercle in the ileum, about 300 cm. from the ileocecal junction.

Autopsy 3411: In the lowermost Peyer's patches about 15 pinhead-sized and somewhat larger yellowish-white opaque tubercles. Microscopically, there were caseous tubercles, with beginning ulceration of the mucous membrane, in the submucosa.

Disease of the cecum was next in frequency to that of the ileum. It was free from disease in only 9 of 80 cases involving the small and large

intestines. In 4 of these the appendix was ulcerated. There were 5 cases of ulceration of the cecum alone and 1 of the cecum and appendix alone. Two cases showed tubercles only. In three cases the lesions were early and few; in one they were moderately advanced and fairly numerous; and in one extensive and far advanced. One case showed an apparently earlier stage of the disease in the ileum in the form of tubercles.

Autopsy 3162: The mucosa of the cecum shows patchy injection, and at one place there is a grapeseed-sized yellow opaque tubercle. The Peyer's patches of the ileum are slightly more prominent than normal, and one small area, slighly elevated and of a dull gray color, shows a small zone of injection around it.

Autopsy 3336: A number of solitary follicles in the lower ileum considerably enlarged and Peyer's patches somewhat swollen. In the cecum a few small, opaque tubercles. Microscopically, some of the lymph follicles of the ileum show numerous recent tubercles.

Autopsy 3080: The cecum contains numerous ulcers with ragged margins, separated by a few islands of intact mucosa, and the ileum a few submucous tubercles.

In 14 cases the ileum and cecum, and in 4 the ileum, cecum and appendix, were involved. The ulcers were more numerous and advanced in the ileum than in the cecum in 9, in the cecum than in the ileum in 4 (in 3 of these the appendix was also involved), and about the same in the ileum and cecum in 5. In 11 cases the entire ileum was involved, with the most advanced and oldest lesions in its lower portion. The lower ileum only was involved in six cases and the upper ileum only in one case. In general, the ulceration was more marked than in involvement of the ileum or the cecum alone. The following case showed extension of the disease from the ileum and cecum to the ileum and jejunum above.

Autopsy 3293: From about the middle of the jejunum to the ileocecal valve the mucous membrane is studded with innumerable pinpoint to pinhead-sized tubercles. In the lower ileum there is one very early, small ulcer. The cecum shows three ulcers, each 1 cm. in diameter.

Among 5 cases in which the jejunum was involved, in addition to the ileum and cecum, there was one in which the lesions were markedly more extensive and advanced in the jejunum than in the ileum or cecum. In one case the seat of the oldest lesions was in the lower half of the jejunum and the upper half of the ileum, and in one case in the cecum. In the

other two cases the lower ileum was apparently the starting point of the disease.

Tuberculous disease of the appendix occurred 44 times (34.1 per cent), with ulcerative lesions in 40 cases. Engelsmann (5) found ulceration of the appendix in 70 per cent and Fenwick and Dodwell (1) in 50 per cent. While disease of the cecum, without involvement of the appendix, occurred in 48 of 86 of our cases, disease of the appendix and other segments of the tract, without involvement of the cecum, was found in only 4 of 42 cases. In the latter the lesions in the appendix were, as a rule, much less marked. In some cases the ulceration in the appendix was apparently a direct extension from the cecum and confined to its proximal part. In the majority of cases the entire mucous membrane, in four cases the distal end, and in one the middle portion was involved.

In general, the lesions in the appendix do not differ from those in other portions of the intestine; but, on account of the peculiar anatomy of the organ, the pathological process may produce marked changes in its gross appearance. It is often thicker than normal and dilated in its distal, more rarely in its proximal and occasionally in its middle portion. It may be deformed by narrowing and partial obliteration of its lumen by healing ulcers. In several cases its appearance suggested beginning gangrene. When opened it was often found filled with thick or thin, yellowish, greenish or brownish, and occasionally hemorrhagic, purulent material.

Four cases with various degrees of ulceration of other segments of the large and small intestine showed tubercles only in the appendix. One case presented tubercles and abscesses in its wall.

Autopsy 3025: Ileum shows several small ulcers and a number of yellow tubercles; the cecum, a number of small ulcers; the appendix, several small yellow foci and two abscess-like cavities in the wall, which do not communicate with its lumen but contain a very thick yellow pus with numerous tubercle bacilli.

Sole ulceration of the appendix was noted in two cases (1.6 per cent). Engelsmann (5) observed ulceration of the appendix alone in 1 per cent of 100, Miloslavich (6) in 1.3 per cent of 300 and Fenwick and Dodwell (1) in 3.8 per cent of 500 autopsies.

Autopsy 3171: Appendix lumen somewhat dilated, about 0.5 cm. from its mouth, and contains a thick, yellow, semifluid material. The tip is obliterated. Microscopic examination of a section through middle of dilated portion

shows normal muscular and peritoneal coats. The mucosa is largely replaced by tuberculous granulation tissue, in which are a number of discrete tubercles.

Autopsy 3289: Appendix 5 cm. long, 0.5 cm. in diamter, and lumen filled with caseous material. Microscopic examination shows ulceration and caseation of a portion of mucous membrane, with caseating conglomerate tubercles in submucosa.

The colon was the seat of ulceration in 63 cases with the following distribution of lesions:

Ascending	18	Ascending and sigmoid	1
Ascending and transverse	11	Ascending and descending	2
Ascending, transverse and descending	7	Transverse	2
Ascending, transverse, descending, sigmoid	10	Transverse and descending	2
Ascending, transverse and sigmoid	1	Descending and sigmoid	1
		Sole ulceration of sigmoid	1
		Not specified	7

One case of ulceration of the lower ileum and of the ileocecal valve showed tubercles only in the colon. Forty-seven out of 63 times ulceration of the colon was associated with involvement of several or all consecutive segments of the intestine above. In only 8 cases was the cecum free from disease (in 2 of these the appendix was involved). In the majority of cases the disease of the colon was apparently an extension of the process from above. In 6 cases the colon appeared to be the seat of the oldest lesions. In 80 per cent of the classified cases the lesions were continuous, involving successive subdivisions of the colon. In the other cases they were peculiarly and irregularly distributed. Ulceration of the colon alone is rare and occurred in only one case with several ulcers, the largest 1 cm. in diameter, located in the sigmoid.

The rectum was involved 15 times, practically always with extensive and advanced disease of the other segments of the tract and always with lesions in various subdivisions of the colon, except in one case in which the ileum and cecum only were ulcerated. The rectum alone was ulcerated in 2 cases.

Autopsy 3062: The rectum shows one small ulcer reaching just below the mucosa. Microscopic examination shows typical tuberculous granulation tissue. At some distance from this area there is a solitary tubercle below the serosa.

Autopsy 3520: One recent tuberculous ulcer about 2 cm. from the anus.

2. Anatomic Changes

The anatomic picture of tuberculous enteritis is usually a multiform one. In many cases may be seen lesions representing the entire course of evolution of the disease, from pinpoint tubercles and minute superficial lesions to large areas of ulceration and destruction of all intestinal coats. There is, however, an earlier stage of involvement, with tubercles in the submucosa, and a hyperplastic and hyperemic condition of the lymph follicles, which is to be noted only microscopically. In some cases, without visible destruction of the mucosa, microscopic examination reveals tubercles which have progressed from the central portion of a follicle, with beginning ulceration of the mucous membrane.

The earliest lesions, whether in the form of miliary or submiliary tubercles or minute ulcers, are located on the summits of the lymph follicles. In only one of our cases were some of the lesions associated with the blood vessels.

Autopsy 3061: Jejunum shows several scattered miliary tubercles definitely associated with the blood vessels. The upper portion of the ileum presents the same picture as the jejunum, in the lower third are miliary tubercles in slightly enlarged Peyer's patches. In one place is a lemonseed-sized ulcer, associated with the blood vessels and not a Peyer's patch. The ulcer is superficial, clean cut and not injected. In the cecum are a very irregular, indurated ulcer, 5 by 2 cm., extending almost to the serosa, and a few small, apparently recent ulcers. Appendix is absent. The colon has, in the ascending portion, a few old and a few recent ulcers, one moderately advanced.

The intestines, in one or more subdivisions or throughout the entire length, may present from one to innumerable ulcers, varying from 1 mm. to several centimetres in diameter. The ulcers are not always regularly and consecutively distributed. They may be grouped in widely separated portions of the same or different segments. Large confluent areas of ulceration, often completely encircling the circumference of the intestine, may be seen alongside of smaller and discrete lesions and tubercles in various stages of degeneration. The mucous membrane often presents a moth-eaten appearance. There may be complete loss of the mucous membrane, except for bands or islands of intact mucosa dividing the lesions. This is most frequently observed in the cecum. No matter how extensive the ulcerated area may be, careful examination will reveal that it is made up of individual lesions of solitary or agminate

follicles. This is more distinctly recognized in the small than in the large intestine.

The shape and direction of the lesions is largely determined by their site. In the jejunum and ascending and transverse colon the ulcers are usually transverse to the long axis of the intestine. In the ileum involvement of Peyer's patches often determines a longitudinal direction. Coalescence of ulcers may give rise to lesions running irregularly in any segment of the tract. As a matter of fact, in advanced tuberculous disease longitudinal lesions are just as common, if not more so than the transversely running lesions said to be characteristic of tuberculous ulceration.

In early stages the ulcers lie opposite the attachment of the mesentery. As they progress along the course of the lymphatics they frequently form

TABLE 4

Showing distribution of ulcers with tubercles in other segments

ULCERATION	TUBERCLES	NUMBER OF CASES
Ileum, cecum, colon	Jejunum	2
Ileum, cecum	Colon	1
Ileum, cecum	Jejunum	1
Cecum	Ileum	1
Jejunum, ileum	Cecum	1
Jejunum, ileum, cecum	Appendix	1
Jejunum, ileum, cecum, colon	Appendix	1
Ileum, cecum	Appendix	1
Ileum, colon	Appendix	1

so called ring or girdle ulcers, which may lead to marked narrowing and stenosis of the lumen, from healing and contraction of the involved area. This condition was not met with in our cases, probably because in secondary intestinal tuberculosis death occurs from the pulmonary disease and its other complications before sufficient healing of such large ulcers takes place. In one case with involvement of the ileum, cecum and colon, and with five active ulcers, one of which completely encircled the lower ileum, there was a marked constriction of the intestine in this region although there was no evidence of healing.

In many cases there are tubercles in various stages of progression, in addition to ulcers in the involved segments. More or less advanced ulceration of one or several segments and tubercles in other regions were noted in 10 cases (table 4).

Coincident with extension along the surface, the tuberculous process may involve successive coats of the intestinal wall and even perforate the serosa. The muscular coat appears to offer a certain degree of resistance to the downward extension of the ulceration. As a consequence, we find that even in very extensive disease the floor of the ulcers is usually formed by the muscularis. Infiltration of the latter with tubercles may give rise to considerable thickening of the intestinal wall.

The mucosa between the ulcers, or that of the nonulcerated segments, very often presents the picture of a chronic or acute catarrhal enteritis. The mucous membrane may show marked hyperemia in patches.

Although the margins and bases of the ulcers are frequently hemorrhagic, active bleeding is rarely met with, because of the obliteration of the blood vessels that is characteristic of the tuberculous process. One of our cases showed a considerable quantity of blood in the intestinal tract at autopsy. It is extremely doubtful, however, whether the hemorrhage was derived from a bleeding ulcer (see autopsy 3125).

General amyloidosis was present in the great majority of our autopsies. as would be expected from the advanced stage and long duration of the pulmonary disease. Amyloid of the intestines was noted in 8 cases, Being part of the general amyloidosis, it was present in early as well as far advanced ulceration, either in the neighborhood of the ulcers only, or involving only one segment or the entire intestinal tract, irrespective of the presence or absence of tuberculous lesions. Only a small proportion of our cases were examined for amyloid degeneration of the intestines, and we believe that careful investigation would reveal that it is present in the majority of cases with marked general amyloidosis.

According to Müller (7) amyloid degeneration of the intestines leads to the formation of amyloid ulcers alongside of tuberculous ulcers. Macroscopically they are practically indistinguishable from each other. The bases of the amyloid ulcers are smooth and glistening and contain blood vessels with hard amyloid walls. They may form extensive girdle ulcers. No study of the occurrence of these ulcers has been made in our cases.

3. Healing

Complete healing of tuberculous ulcers without the presence of active lesions is extremely rare and was found in only one of our 199 autopsies.

Autopsy 3096: Most of the intestine shows considerable contraction. In the upper ileum there is what appears to be a healed ulcer. The mucosa of

the lower ileum shows fine gray scars over a considerable extent. The mucosa of the cecum and ascending colon also shows a number of fine gray scarred areas.

Healed ulcers in one segment and active ulceration in another was noted in one case.

Autopsy 3125: Ileum has prominent solitary follicles. In lower and middle portions are several scarred, pigmented areas, suggesting healed ulcers. Cecum shows numerous small erosions and superficial ulcers, up to 5 mm. in diameter. The mucosa of the cecum and colon shows large blood-stained patches and the cecum, colon and rectum contain considerable blood.

Scars suggesting completely healed ulcers, with active lesions in the same or other segments of the intestines, were observed in numerous cases. A tendency to healing, often quite marked, is common. Ulcers classified as healing, well healed and almost healed were noted in 14 cases. In some of these there were also healed lesions in the same or other segments of the tract.

Healing and healed ulcers were noted in all parts of the intestine, but were most frequent in the ileum and cecum, probably because these segments are usually the seat of the oldest lesions. The healing process is most often observed in the central portion or on one side of an ulcer, with progression of the lesion around it or on the opposite side.

From an analysis of these cases it appears that tuberculous ulcers of the intestines may heal completely and that the disease may at the same time, or perhaps subsequently, attack other areas of the same or other segments of the tract, and that some ulcers may show well advanced healing while others are markedly progressing in the same region of the intestines.

Healing ulcers were much more rarely met with in cases with early, small and few lesions or in those in which the ulceration was limited to one segment, than in cases with widespread and far advanced involvement. This may probably be explained by the longer duration of the disease in the latter cases. There was no evidence to show whether or not completely healed lesions subsequently become active and progressive. As has been stated above, stenosis or marked narrowing of the lumen of the intestine, as a result of healed and contracting ulcers, was not met with in our cases.

4. Perforation

Perforation is rather infrequent if compared with the large number of lesions found at autopsy. This is due to several characteristics of the tuberculous process in the intestine. First, with the progression of the ulcers toward the serosa the tissues of their bases become thickened by inflammatory processes and by fresh and closely aggregated tubercles; second, there is a tendency to the walling off of deep ulcers by a localized peritonitis of the overlying serosa and a matting together of loops of the intestine with one another and with the omentum; and, finally, advanced intestinal ulceration is, as a rule, a complication of advanced phthisis, and death from exhaustion or other complications usually supervenes before the ulcerating process reaches and destroys the serosa.

Perforations were noted in only 4, or about 3 per cent, of our cases. They occurred in the jejunum in two cases, in the ileum in two cases and in the rectum in one case. Two of these showed widespread and advanced ulceration of practically the entire tract, from the jejunum to and including the rectum, while one was of the ileum and cecum and one of the ileum alone. In another case, not included in the above, the tip of the appendix was perforated, its lumen communicating with an abscess cavity that was completely walled off by firm adhesions, and there was no general peritonitis.

Fenwick and Dodwell (1) report 1.2 per cent of perforations in 2000 cases. It is interesting to note that they found 10 per cent of them in the duodenum, with an incidence of ulceration in this segment of 3.4 per cent. In their series of cases the ileum (1.1 per cent) and the jejunum (0.53 per cent) were the next most frequent seats of this complication. Perforations are rare in other segments of the tract. It is probable that many are hidden by adhesions between loops of the intestines, or are covered up by adherent omentum and thus escape detection at autopsy.

The occurrence of perforations does not appear to have any demonstrable relation to the severity or extent of involvement. In every instance the perforations were associated with a general fibrinopurulent peritonitis. Extravasation of the intestinal contents into the peritoneal cavity was not observed.

5. The Peritoneum

On opening the abdomen the position and extent of tuberculous ulcers are, in the majority of cases, clearly indicated by areas of peritonitis of the overlying serosa. The latter presents patches of tuberculous in-

flammation, bright or deep red, and granular in appearance, due to clusters of tubercles in dilated lymphatics. As a rule this localized peritonitis is the more pronounced the deeper the ulceration has extended toward the serosa; but it is quite common with very superficial lesions. On the other hand, the serosa frequently presents a normal, glistening appearance or only clusters of pearly, white tubercles, with extensive and advanced ulceration of the intestine. In some cases the serosa of an entire segment or of the greater part of the whole intestine is deeply and more or less uniformly injected. In deep seated ulcers it often presents a puckered appearance.

In more advanced stages of enteroperitonitis the serosa is covered, in patches, by a fibrinopurulent exudate. This may become organized and lead to thickening of the serosa and subserosa. Loops of the intestine may become adherent to one another and to the omentum. There may or may not be an effusion into the peritoneal cavity. The peritonitis may become generalized, with ascites of from less than 100 cc. to several litres. The fluid in these cases is usually serous or turbid, with flakes of fibrin floating in it, but it may be distinctly purulent. This form of peritonitis was present in 7 cases. The most severe forms with fibrinopurulent effusion occurred in the cases with perforation.

Autopsy 3074: The midportion of the jejunum shows numerous far advanced ulcers. A few of these are perforated. The ileum has recent and moderately advanced ulcers throughout its entire extent, most marked in and about the ileocecal valve. The cecum and appendix show advanced ulceration. The ascending colon has a few small, moderately advanced ulcers. The serosa of the small intestine shows numerous areas of patchy injection, with tubercles in the lymphatics. The peritoneal cavity contains several litres of pale, yellow fluid, in which float flakes of fibrin which also cover most of the visceral and parietal peritoneum. The omentum is plastered to many loops of the intestine by a fibrinopurulent exudate, which in places is partially organized.

Autopsy 3126: In the ileum are ragged ulcers extending into the muscularis. One ulcer, a foot from the ileocecal valve, shows a perforation 4 mm. in diameter. The ulcers are most numerous just above the valve. The cecum has a few superficial recent and old ulcers. The serosa corresponding to the ulcers shows groups of miliary tubercles. The entire small intestine is covered by a fibrinopurulent exudate. The abdomen contains several litres of turbid, yellowish-green fluid, with flakes of fibrin floating in it. Some of the loops of the intestine are matted together by fibrinopurulent exudate, but they are readily separated. The exudate also covers the abdominal organs.

Autopsy 3161: The jejunum in its entire length, shows numerous advanced ulcers, separated from one another by a distance of from a few to 10 cm. The bases extend deep into the muscularis and, in a number of cases, to the serosa, the lymphatics of which contain numerous gray tubercles. The bases of the ulcers are necrotic. The lower jejunum shows a number of short loopings, with the bases of ulcers adherent to one another by masses of fairly tenacious fibrinopurulent exudate. The omentum is also adherent to the bases of many ulcers. A few ulcers are perforated. The ulcers in the upper portion of the ileum are similar to those in the jejunum, but are not so numerous. For 2.5 feet, beginning just above the ileocecal valve, the mucosa is thin, delicate and unbroken. Just above the ileocecal valve there is a large area of irregular ulceration, extending deeply into the intestinal wall and continuing over the valve into the cecum. In the cecum are numerous advanced, irregular ulcers similar to those in the jejunum. The ascending and transverse colon has a considerable number of similar ulcers. The appendix is bound down to the cecum by tenacious fibrinopurulent exudate. It contains a thin, purulent fluid and its mucosa shows extensive ragged ulcers throughout. In the rectum are five ulcers, from a few millimetres to 2 cm. in diameter. The tissues about the large ulcers are infiltrated, and one of the more advanced ulcers shows a perforation into the peritoneal cavity. The parietal peritoneum shows almost everywhere patches of injection, and is of a dull appearance. There are 1200 cc. of turbid, yellow fluid containing masses of fibrinopurulent exudate. Loops of intestine and structures in the pelvis are adherent to one another by the same kind of exudate.

Autopsy 3541: About the middle of the ileum are several ulcers extending through the peritoneal layer. In places, coils of the intestine are matted together by fairly firm fibrinous adhesions. Separation of the adherent coils of the ileum discloses a perforation about 2 mm. in diameter, surrounded by organizing fibrinopurulent exudate. The peritoneal surface of the intestine is covered by the same kind of exudate. The pelvis contains a large amount of purulent fluid.

In several of our cases there were healed adhesions between the abdominal organs and portions of the intestine, without effusion and probably the result of a chronic, low grade tuberculous enteroperitonitis. In a few cases the parietal peritoneum showed tubercles.

The mesentery occasionally presented from a few to very numerous tubercles. In one case the nodules were so large as to give the appearance of tabes mesenterica.

Tuberculosis of the mesenteric lymph nodes was observed in the majority of our cases. In about 10 per cent caseation was noted. In

several cases many of the nodes showed calcification. The changes in the mesenteric nodes do not appear to bear any relation to the severity and extent of the intestinal involvement.

6. Site of Earliest Localization

It is stated by many clinicians and pathologists that secondary intestinal tuberculosis results from invasion of the tract by tubercle bacilli swallowed with the sputum. The theory of the enterogenous channel of infection is based largely on the observation that the first lesions have their seat almost invariably in the ileocecal segment of the intestine. This region is rich in lymph follicles for which tubercle bacilli appear to have a special predilection. Here the acid reaction of the chyme becomes alkaline, and inspissation and a slowing up and stagnation of the intestinal contents take place. This is said to permit the bacilli to remain in prolonged and intimate contact with the mucous membrane and to penetrate into the lymph follicles.

That tubercle bacilli pass through the intestinal tract for years without giving rise to infection is explained by the assumption of a failure of local resistance. That lessened resistance of the mucous membrane probably plays an important part is evidenced by the fact that tuberculous ulceration of the intestine is practically always a complication which sets in late in the course of chronic phthisis.

Enterogenous infection does not, however, explain some cases, particularly those in which the jejunum is more severely and extensively diseased than the ileum, or in which the ileum or its lower portion is free from disease, or in isolated ulceration high up in the small intestine associated with lesions in the colon, or in certain cases in which discrete ulcers of apparently the same age are distributed over a large part of the intestine and in isolated ulceration of various portions of the tract other than the ileocecal region. In these cases a hematogenous origin of the disease must be considered.

There are many facts which indicate that the tuberculous process usually starts in the ileocecal region. The earliest lesions, whether in the form of tubercles or beginning ulceration, were practically always limited to the ileum or the cecum in our cases. In general, the ileum and the cecum were the most frequently diseased segments of the intestine. In widespread disease it is the lower ileum or the cecum which is usually the seat of the oldest and most advanced lesions. In over 36 per cent of all

cases the ulcers were limited to the ileum or cecum or to both with or without disease of the appendix. In 500 cases reported by Fenwick and Dodwell (1) the last foot of the ileum and the contiguous portion of the cecum was the seat of ulceration in 85 per cent. As a matter of fact, ulceration above the ileum and of the colon, without disease of the cecum or ileum or both, is apparently so infrequent that the dictum of Westenhöfer (8), that if there is no involvement of this region there is no intestinal tuberculosis, may be accepted with but a small element of error.

As to whether the disease starts in the lower part of the ileum or in the cecum, it appears probable, from an analysis of our cases, that it is in the former region that the earliest localization of the tuberculous process occurs. There were a number of cases in which the lower ileum was free from disease and in which the oldest ulcers were in the cecum. The latter was also the seat of the oldest and most advanced disease in a number of cases in which the lower ileum was involved. In a few cases the ileocecal valve was the location of the most advanced and oldest ulceration. That the lesions may have their starting point elsewhere is evidenced by the few instances of sole ulceration of the jejunum, appendix, colon and rectum.

From the seat of earliest localization in the ileocecal region the portions of the tract above and below become involved. Progression of the disease to the large intestine appears to occur earlier than to the small intestine. Thus, in 86 cases, in which the ileum and other segments of the tract were ulcerated, the large intestine was involved 80 times and the small intestine above the ileum only 44 times. Furthermore, ulceration of the ileum and of other segments of the small intestine occurred in 6 cases and of the ileum and the large intestine in 42 cases. In explanation of this, and the comparatively more extensive ulceration occasionally found in the colon, it has been suggested that the lower portions of the tract are infected by bacilli from lesions higher up which are more virulent than those weakened by passage through the acid contents of the stomach. Extension of the involvement upward is difficult to explain by enterogenous infection although it has been shown that bacteria may be carried from the cecum against the direction of peristalsis.

II: CLINICAL OBSERVATIONS

1. Correlation of Clinical Course and Anatomic Changes

The clinical course of 127 of our ulcerated cases shows that only 49 presented symptoms referable to the intestinal tract. In order to study the relatons between the ulceration *per se* and the symptomatology we have divided our cases into five groups (table 5).

TABLE 5

Showing proportion of cases in which a clinical diagnosis was made and the frequency of the usual symptoms

	TOTAL NUMBER	NUMBER DIAGNOSED CLINICALLY	DIARRHEA	DIARRHEA ALTERNATING WITH CONSTIPATION	REGULAR BOWELS	MODERATE CONSTIPATION	MARKED CONSTIPATION	COLICKY PAIN	TENDERNESS TO PALPATION	RIGIDITY OF ABDOMINAL WALL	PALPABLE TUMOR	BLOOD IN STOOLS
Group 1												
Duodenum, jejunum, ileum	1				1							
Jejunum, ileum	6	1	1		2	1	2					
Jejunum	1				1							
Ileum	20	6	6	4	10	4		4	3	3		
Small intestine (no detail)	2	1	1			1						
Group 2												
Cecum	5	1	1		4							
Cecum, appendix	1	1	1					1	1	1		
Cecum, appendix, colon	2	2	2					2	1	1		
Cecum, appendix, colon, rectum	1	1	1					1				
Cecum, colon	3	2	2		1			2	1	1	1	
Cecum, colon, rectum	1	1	1									
Ileum, appendix	1						1					
Appendix	2				2							
Sigmoid	1				1							
Rectum	2	1	1	1		1						1
Group 3												
Ileum, cecum	11	2	2		5	3	1	2	1	1	1	
Ileum, cecum, appendix	4	3	2		2			3	3	2	1	
Jejunum, ileum, cecum	4	1	1		2	1		1				1
Jejunum, ileum, cecum, appendix	1	1	1					1		1		

TABLE 5—*Continued*

	TOTAL NUMBER	NUMBER DIAGNOSED CLINICALLY	DIARRHEA	DIARRHEA ALTERNATING WITH CONSTIPATION	REGULAR BOWELS	MODERATE CONSTIPATION	MARKED CONSTIPATION	COLICKY PAIN	TENDERNESS TO PALPATION	RIGIDITY OF ABDOMINAL WALL	PALPABLE TUMOR	BLOOD IN STOOLS
Group 4												
Duodenum, jejunum, ileum, cecum, colon..	1	1	1					1				
Duodenum, jejunum, ileum, appendix, colon.	1	1	1	1				1		1		
Jejunum, appendix, colon, rectum.....	1	1	1									
Jejunum, ileum, cecum, colon.....	8	4	3		3	2		3	2			
Jejunum, ileum, cecum, appendix, colon....	11	5	3	2	7		1	5	4	4		
Jejunum, ileum, cecum, colon, rectum.....	1	1	1					1	1	1		
Jejunum, ileum, cecum, appendix, colon, rectum.....	6	3	3	1	1	1	1	3	2	2	1	
Jejunum, ileum, colon.....	1				1							
Ileum, cecum, appendix, colon.....	6	1	1		5			1				
Ileum, cecum, appendix, colon, rectum.....	2				2							
Ileum, cecum, colon.....	11	4	2		7		2	2	2	2		1
Ileum, cecum, rectum.....	1	1	1					1	1			
Ileum, colon.....	5	2	2	1	2		1	2	1			
Small and large intestines (no detail).....	1				1							
Group 5												
Intestines (no detail).....	2	1	1		1			1				
Tubercles in ileum.....	2	1	1		1			1	1	1		
Tubercles in cecum.....	2				2							
	131	50	44	10	64	14	9	39	24	21	4	3

Group 1: 30 cases of ulceration limited to the small intestine. Of these, 22 presented no symptoms either before admission or during the period of observation. In 20 the bowels were regular or there was slight or moderate chronic constipation. Severe constipation during the terminal stage of the disease was noted in 2 cases. Diarrhea was a prominent symptom in 8 cases, in 6 of which the ileum alone was diseased. In 4 of the latter the diarrhea alternated with constipation.

Abdominal pain and diarrhea occurred in 3 cases of disease limited to the ileum. In one the duration of pulmonary disease was about three years, of period of observation nine months and of symptoms six months. At autopsy a severe fibrinopurulent peritonitis and several perforations were found (see autopsy 3541). In the second case, observed for one year and five months, these symptoms set in three months before exitus.

At autopsy there were found a moderate number of small recent ulcers and a few yellow tubercles in the upper and middle portions of the ileum. The peritoneal surface of the intestine was not involved. In addition to the tuberculous lesions there was a typical, rather deep, round ulcer of the stomach near the beginning of the pylorus. The duration of the pulmonary disease in this case was about three years. The third case, with severe abdominal pain and diarrhea for three months before exitus, showed several moderately advanced ulcers near the cecum. In the first two cases there was also marked tenderness to palpation and rigidity of the abdominal wall. All the four symptoms were noted in a case with two small, recent ulcers in the lower portion of the ileum, chronic passive congestion of the large intestine and 900 cc. of turbid fluid in the abdomen, with a floccular fibrinopurulent deposit over portions of the small intestine. The duration of the symptoms was about three months and of the pulmonary disease about 3 years.

That the character of the lesions and the extent of the disease in the intestine or the degree of involvement of the peritoneum had very little, if any, relation to the symptomatology may be illustrated by the following typical cases. One, with severe diarrhea for two months before exitus, showed at autopsy one moderately advanced ulcer in the midportion of the jejunum and one in the midportion of the ileum. On the other hand, in another case under observation for five and one-half months, with a large number of advanced ulcers from the beginning of the jejunum to the ileocecal valve, the bowels were always regular. The degree of involvement of the peritoneum in these cases corresponded to the severity of the intestinal ulceration.

Group 2: 18 cases with the disease limited to the large intestine. In ulceration limited to the cecum the disease appears to run a latent course. Three cases with few and early lesions, and the most advanced case with tubercles in the ileum and nearly complete destruction of the entire mucosa of the cecum (see autopsy No. 3125), presented no symptoms. The periods of observation were two weeks, one and one-half months, two months and three years, respectively, and the duration of the pulmonary disease from one and one-half to eleven years. In the one case with diarrhea setting in one month before exitus, there were a few recent, small ulcers in the cecum and a chronic passive congestion of the jejunum and ileum. One case with numerous large, recent ulcers in the cecum and small recent ulcers in the appendix, without

involvement of the serosa, presented diarrhea, colicky pain, tenderness to palpation and slight rigidity of the adominal wall.

There were 7 cases of ulceration of the cecum and colon, some with and some without disease of the appendix and rectum. Diarrhea was present in 6, colicky pain in 5, tenderness to palpation of the abdomen in 2 and rigidity of the abdominal wall in 2. The cases were under observation for from two months to over one year. The symptoms set in from two to four months before exitus.

In all cases, including the one which ran a latent course, the ulceration in the cecum was extensive and advanced. In 2 cases the ulceration extended not more than 1 cm. into the ascending colon. In the others the greater part of the entire colon was involved. The case which presented no symptoms was under observation for one month and nineteen days, and presented at autopsy numerous large ulcers in the cecum and the colon to about its descending segment. The peritoneal surface was injected and there was an early serofibrinous peritonitis. In one case a definite cecal tumor was palpable clinically but nothing to explain it was found at autopsy.

One case, with numerous, recent, small ulcers in the last 10 inches of the ileum and a small ulcer near the tip of the appendix, was severely constipated during the period of observation of eight and one-half months.

The 2 cases of sole ulceration of the appendix (see autopsies No. 3171 and No. 3289) and the one case of involvement of the sigmoid alone ran a completely latent course.

Of the 2 cases of sole ulceration of the rectum (see autopsies No. 3062 and No. 3520), one presented severe diarrhea alternating with constipation, and blood in the stools for about five months before exitus, and the other moderate constipation during a period of observation of over four months before death. The difference in the symptoms is difficult to explain by the autopsy findings.

Group 3: 20 cases of involvement of the small intestine and the cecum with and without the appendix. Twelve of these cases ran a completely latent course with regular or moderately constipated bowels. In one case under observation for eleven and one-half months, with numerous advanced ulcers of the ileum and cecum, constipation was marked for several months before exitus. The case which at autopsy was found to have suffered a perforation with the presence of a severe fibropurulent peritonitis (see autopsy No. 3126), presented no symptoms referable

to the intestinal tract or of a peritoneal complication. Among the latent cases was also one with tuberculous abscesses in the wall of the appendix (see autopsy No. 3025).

Diarrhea was present in 6 cases, colicky pain in 7, tenderness to palpation and rigidity of the abdominal wall in 4, cecal tumor in 2 and blood in the stools in 1. In a case under observation for over two and one-half months, showing extensive, advanced ulceration of the lower ileum, cecum and appendix, the bowels were always regular, and a diagnosis was made on severe abdominal pain, tenderness to palpation and rigidity of the abdominal wall.

There were two cases of enteroperitonitis in this group. In one of these there was a palpable tumor in the ileocecal region. At autopsy a nodular, retroperitoneal mass was found to the left of the cecum, in which the appendix was embedded and firmly attached to the surrounding tissues. The appendix was severely ulcerated. This was the only case in which the pain was always localized at McBurney's point. In the other case with a palpable mass the ileocecal valve was considerably thickened.

In the cases in which the appendix was diseased a combination of all symptoms occurred in more cases than when this organ was not involved. The degree of disease in the ileum and jejunum, and whether one of these segments or both were ulcerated, had apparently no bearing on the symptomatology. The same may be said of the involvement of the cecum. In 3 cases with symptoms the ulcers in the cecum were few in number and recent and in 3 there was practically complete destruction of the mucosa. In the cases without symptoms a similar proportion of early and far advanced disease of the cecum was noted.

Group 4: 56 cases of ulceration of the small and the large intestine. The overwhelming majority of these cases showed at autopsy widespread disease of several or all segments of the small and large intestine, with numerous lesions in all stages of progression and varying degrees of involvement of the serosa. Only 24, however, presented symptoms referable to the intestinal tract.

Diarrhea was present in 19 cases, colicky pain in 20, tenderness to palpation of the abdomen in 13, rigidity of the abdominal wall in 10, palpable tumor in 1 and blood in the stools in 1. In 5 cases the bowels were regular or markedly constipated and the diagnosis was made on some or all of the other symptoms.

In this group, unlike the previous group, diarrhea occurred in a considerably greater number of cases of ulceration involving the jejunum and ileum (14 of 30) than the ileum alone (6 of 25). The severity of disease of the cecum and ascending colon did not appear to have any relation to the occurrence of this symptom. The number of cases with diarrhea apparently increased in proportion to the number of segments of the colon involved. There is some indication that ulceration of the rectum had some bearing on the presence of diarrhea.

Group 5 includes one case with tubercles only in the lower ileum which presented all the symptoms in a marked degree, leading to a clinical diagnosis of extensive ulceration of the intestine.

2. Etiology of Symptoms

Various theories have been advanced to explain the presence or absence of diarrhea and colicky pain in tuberculous ulceration of the intestine. According to Nothnagel (9) diarrhea depends on interference with the absorption of water from the colon below the first portion of its ascending segment, and hence on the seat of the lesions. Ulceration limited to the small intestine, the cecum and the first portion of the ascending colon probably never produces diarrhea unless the disease is complicated by certain other conditions, as catarrh of the intestine, amyloid disease, special forms of infection or other factors that exercise a direct influence on the peristaltic movements of the bowels, because so long as the rest of the colon is healthy there is no interference with the absorption of water from the intestinal contents and because increased peristalsis to produce diarrhea must involve the small and the large intestine or the latter alone. On the other hand, ulceration of the lower segments of the colon and of the rectum invariably causes diarrhea because destruction of the mucous membrane interferes with the absorption of water. There may therefore be no diarrhea if there are only a few ulcers in the colon; and it may be absent in cases of severe and extensive disease of the colon, because the irritability of the nerves having become inhibited or abolished by marked destruction of the intestinal wall, there is no accelerated peristalsis.

Bandelier and Roepke (10) say that diarrhea and colicky pain depend primarily upon increased peristalsis caused by irritation of the nerves exposed by the ulceration and secondarily on the seat of the lesions.

Leupold (11) investigated 23 cases of tuberculous ulceration of the intestine and found that in the 7 cases in which diarrhea was a clinical

symptom the plexuses of Auerbach were markedly involved by perineural and periganglionic round cell infiltration, while such changes were present in only 3 of the 16 cases without diarrhea. The round cell infiltration in the former cases extended beyond the limits of the ulcers and was noted in connection with a greater number of lesions than in the latter. He concluded that the inflammatory process in the plexuses of Auerbach probably gives rise to increased peristalsis and to diarrhea but that other factors must be taken into account.

Fleiner (12) maintains that the symptoms of ulceration correspond largely to the intensity of the irritation of the nerves at the bases of the ulcers. This irritation may produce motor symptoms such as peristaltic unrest, diarrhea or spastic constipation, and sensory symptoms as colicky pains.

Schmidt (13) does not believe that diarrhea and pain are caused by irritation of the nerves. Our knowledge of the innervation of the intestinal wall and of the sensory fibres of the mucous membrane, he says, is too limited for such an assumption. According to him the condition of the mucous membrane between the ulcers alone determines the presence or absence of diarrhea.

If we attempt to correlate the above theories with the symptomatology of our cases we find that none of them fully explains their clinical course. It appears that the presence or absence of diarrhea and colicky pain is determined largely, if not altogether, by conditions other than the number, size, seat and depth of the ulcers. What these conditions are is difficult to state definitely. The most important are probably amyloidosis and toxemia. Diarrhea is a symptom of general amyloidosis and may be severe and persistent when this process involves the intestine. Fishberg (14) says that diarrhea in advanced phthisis may be due to elimination through the intestine of toxins circulating in the blood.

Diarrhea may also be due to the irritating action of various articles of diet, particularly when they reach the intestine in an insufficiently digested or undigested state, to swallowed sputum, to errors of diet and overfeeding, and to faulty digestion due to secretory or motor insufficiency of the stomach. In all these forms of gastrointestinal irritation the intestine sooner or later becomes the seat of catarrhal changes, which probably play an important rôle in the causation of diarrhea and colicky pain in many cases.

Colicky pain may be due to violent peristaltic contractions of the intestine as a result of the irritation of the nerves at the bases of the

ulcers. Most probably, however, it is a reflex symptom due to mechanical irritation of the inflamed serosa and to catarrhal conditions of the mucous membrane. Pain and tenderness to palpation of the abdomen is probably also of reflex origin. It occurs with the greatest frequency in cases with widespread and severe involvement of the serosa.

Taking into consideration all the theories at our disposal, it still remains impossible to explain the latent clinical course of so many cases, unless we assume that tuberculous ulceration of the intestine, like pulmonary tuberculosis, may run a symptomless course for a considerable period, in the presence of marked tissue destruction, and that many cases would ultimately develop symptoms, were it not for their termination from asthenia and other complications of the pulmonary disease.

3. Diagnosis

A clinical diagnosis of tuberculous ulceration of the intestine cannot, as has been shown above, be made in the majority of cases. Other observers have also reported the same conclusion. In Engelsmann's 100 cases (5) a clinical diagnosis was made in 32. In our 127 cases the intestinal complication was recognized in 49 or 36.8 per cent.

Walsh (3), from a study of 100 cases, concluded that diarrhea, colicky pain, tenderness to palpation of the abdomen and rigidity of the abdominal wall, are of very little significance in the diagnosis, because some or all of these symptoms occurred in as many of his cases without ulceration at autopsy as with it, and that they signify an enteritis but not a specific ulcerative enteritis. This observation does not coincide with our findings. Diarrhea and colicky pain were noted in only five of our cases without ulceration. The diarrhea was, however, not persistent and was easily controlled by diet and medication. The colicky pain was never marked and occurred only occasionally for brief periods. In none of them were any of the other symptoms noted.

Although the presence of tuberculous ulcers in the intestine cannot be ruled out by the absence of symptoms, it may be said, with a negligible degree of error, that diarrhea in far advanced phthisis, especially in cases with laryngeal ulceration, becoming more and more persistent and uncontrollable, practically always justifies a diagnosis of this complication. If, in addition, there are colicky pain and meteorism, the diagnosis is certain.

In the great majority of our cases diarrhea was the first symptom to call attention to the presence of an intestinal complication. Colicky

pain is usually a later symptom, but it may set in a considerable time before diarrhea or it may remain the most prominent symptom with regular bowels or with severe and obstinate constipation.

Pain on deep palpation, especially if it is persistently localized, is a very suggestive sign of ulceration. In the ileocecal region this symptom may be interpreted as indicating disease of, but not necessarily confined to, this segment of the intestine.

Marked rigidity of the abdominal wall is always a sign of severe involvement of the serosa or of general peritonitis with effusion. Although the milder degrees of localized and general peritonitis, with small and moderate effusions, often remain unrecognized clinically, the more severe types of fibrinopurulent peritonitis, as a rule, present marked signs. In several of such cases, including one with perforation, the condition was unsuspected clinically.

Palpable tumor is comparatively rare. When this condition is observed in the ileocecal region it must be kept in mind that enlarged lymph nodes and the presence of feces may simulate thickening from tuberculous hypertrophy and infiltration of the intestine.

There is nothing characteristic of the stools. Blood is a comparatively infrequent symptom. It is usually mixed with the feces and, if present, is a corroborative sign when associated with other suggestive symptoms. Frank hemorrhage from the bowels did not occur in any of our cases. Profuse and uncontrollable bleeding, causing rapid exsanguination and death, has been reported by Engelsmann (5) and Cruice (15).

Constipation of varying degrees is so frequently met with in patients with chronic phthisis that no very definite conclusions can be drawn as to the relation of this irregularity of the bowels to tuberculous ulceration of the intestines. At any rate, it does not appear from our cases that it can be correlated with involvement of any particular segment of the tract. Severe constipation occurred in as many of our cases with ulceration as without it, and in disease of the large and small intestines as well as of the small intestine alone. However, the onset of severe constipation in a patient in whom the bowels had previously been regular, associated with marked and rapid failure of nutrition and an irregularly elevated temperature, should direct attention to the possibility of an intestinal complication. No relation of obstinate constipation to healing ulceration and contraction of the intestine could be established in our cases.

The seat of the lesions cannot be determined from any of the known clinical symptoms. Such symptom complexes as have been worked out by Archibald (16), as diagnostic of disease of certain segments and combinations of segments, are, in our experience, without the slightest value.

Although diarrhea appears to be a characteristic symptom of ulceration of the large intestine, it may be present in disease of any of the segments of the tract and is therefore of no value in localizing the lesions.

As a general rule it indicates widespread involvement of the small and large intestines. We are unable to conclude that constipation is of any significance as pointing to ulceration of the small intestine alone, and that diarrhea alternating with constipation is diagnostic of disease of the small and large intestines. There are many reasons unrelated to the location of the lesions which explain the occurrence of periods of constipation in cases treated symptomatically for tuberculous diarrhea.

What has been said of diarrhea as a localizing symptom applies with even still greater force to the other clinical symptoms. Blood in the stools, said to be characteristic of ulceration of the rectum, may occur in disease of any portion of the intestine. As a rule it is impossible to determine, even at autopsy, the source of the bleeding.

From the attitude of Walsh (3), that a diagnosis of intestinal tuberculosis "cannot be made with the slightest degree of certainty from our present known symptoms," the pendulum has swung in the opposite direction. The position taken now is that the symptoms, on which a diagnosis had heretofore been considered justifiable, manifest themselves in the advanced and hopeless stages of the intestinal disease and that a diagnosis of even beginning ulceration can be made in any stage of the pulmonary disease on other symptoms and by the roentgen ray.

Paterson (17) says that it is as fallacious to wait with the diagnosis until diarrhea develops as it is to delay the diagnosis of pulmonary tuberculosis until tubercle bacilli are found in the sputum or until definite signs of a cavity in the lung are present. Although this may be perfectly true from an academic standpoint it is doubtful whether we are able to make a definite clinical diagnosis in the majority of cases until this symptom appears.

Diarrhea does not always indicate advanced tuberculous ulceration. It is present to a very marked degree in cases with few and very early lesions, limited to a small segment of the intestine. Instead, it may be said that diarrhea and the other symptoms, as a general rule, begin to

manifest themselves in the advanced and terminal stages of the pulmonary disease, irrespective of the severity and extent of the intestinal complication. In the great majority of our cases the onset of symptoms occurred within from three to six months before exitus. In only a few cases were they present for a longer period and in no case for over one year.

The early diagnosis of tuberculous enteritis is based largely on constitutional symptoms and gastrointestinal disturbances of a dyspeptic character. Fishberg (14) says that progressive loss in weight, in patients with improving or stationary lung lesions, usually indicates intestinal tuberculosis. According to Brown and Sampson (18), "when any patient even in an incipient stage begins to do poorly, shows no increase of pulmonary symptoms and signs, or even, what is more important, a lessening of signs and symptoms referable to the lungs, intestinal complications should be borne in mind;" and that intestinal involvement becomes more probable if, in addition, the patient exhibits symptoms of derangement of the gastrointestinal functions such as "constipation, slight loss of appetite, slight dyspepsia, a feeling of fulness or discomfort in the abdomen after eating, in all probability accompanied by gas."

There is no doubt that it would be desirable to recognize the intestinal complication early and in its earliest stages, particularly in favorable cases of pulmonary tuberculosis when therapeutic measures might possibly still be of avail. It is extremely doubtful, however, whether the above vague and indefinite symptoms of dyspepsia justify a diagnosis on which radical therapeutic measures would be permissible. In the early stages of pulmonary tuberculosis it is much more probable that they are due to overfeeding and the sedentary life which tuberculous patients usually lead rather than to ulceration of the intestine. Under these conditions patients may do poorly for considerable periods without any apparent increase in the pulmonary signs and symptoms and improve rapidly on a well regulated diet, exercise and change of environment.

The frequency of intestinal tuberculosis in the incipient and early stages of the pulmonary disease is difficult to determine. We believe that it is rather rare. Among the last 2000 patients admitted to Bedford Sanatorium, the great majority of whom were early and moderately advanced favorable cases, clinical symptoms on which a diagnosis of this complication could be ventured were present in 16, of which 5 were moderately advanced, rapidly progressive, and 11 far advanced. Among

the far advanced patients in the wards of the Montefiore Hospital about 25 per cent present definite symptoms of tubercuolus enteritis.

In the advanced stages of the pulmonary disease it is obvious that a diagnosis of intestinal tuberculosis will prove to be correct in the great majority of cases. Any symptoms or group of symptoms may therefore be correlated with the intestinal complication in the terminal stages of chronic phthisis. It still remains to be determined, however, what symptoms definitely indicate tuberculous ulceration of the intestine, early or advanced until the classical symptoms set in.

The character of the temperature in cases with intestinal ulceration is usually that of the pulmonary disease. Saugman (19), however, has pointed out a type of fever which in our experience is strongly suggestive of intestinal tuberculosis. It is an irregularly irregular temperature, with the curve of one day entirely different from that of the other coming on in the terminal stages of the pulmonary disease. If, in addition, there is a rapid, downward course, the probability of this complication is greatly increased, even in the absence of all symptoms referable to the gastrointestinal tract. As a general rule, the bowels in these cases are constipated. Saugman also states that in the earlier stages of pulmonary tuberculosis this type of temperature is frequently a sign of tuberculous enteritis.

The laboratory offers no definite aids in the diagnosis. The presence of tubercle bacilli and of occult blood in the feces is now generally recognized as being of no value.

There remains yet to be spoken of the roentgen diagnosis of tuberculosis of the intestine. Stierlin (20) was the first to call attention to hypermotility of the contents of the colon in tuberculous ulceration of the large intestine. Béclére and Mériel (21) published the same observation in 1912. In this country, Pirie (22) noted an abnormally rapid emptying of the barium meal from the cecum in cases of tuberculosis of this segment.

Brown and Sampson (18) since then have taken up this work, and from their observations have concluded that hypermotility, ileac stasis and filling defects are characteristic of ulceration of the cecum and ascending colon and that tuberculous colitis can be definitely diagnosed in all stages by the roentgen ray. They say that the absence of certain shadows cast by the barium meal, however, does not absolutely exclude colonic tuberculosis and that a diagnostic roentgenological picture of disease of the small intestine is still to be found.

At the Montefiore Hospital we have attempted to apply the X-ray in the diagnosis of intestinal tuberculosis, checking up a number of cases with autopsy findings. So far our results have not been uniformly convincing as to the alleged great value of this method of diagnosis. In some cases with numerous ulcers in various parts of the intestine the emptying of the cecum proceeded normally. Conversely, in many cases without ulceration the hypermotility of the bowel was quite marked. Our study of the subject is being continued and our final conclusions will be published subsequently.

4. Prognosis and Treatment

Our experience with tuberculous ulceration of the intestines has been confined largely to its occurrence in advanced phthisis. In this stage of the pulmonary disease the onset of definite clinical symptoms of an intestinal complication always marks the beginning of a rapid and fatal termination.

In advanced pulmonary tuberculosis treatment of tuberculous enteritis means the relief, as far as possible, of symptoms. Unfortunately, the most distressing of these, diarrhea, is as a rule very little influenced by the therapeutic measures at our disposal. The most valuable remedy we possess is calcium chloride which, given intravenously, has been effective in some cases in relieving diarrhea and pain. Its use was first proposed by Saxtorph (23). Fishberg (24) and Ringer and Minor (25) have reported favorable results.

Operative interference in advanced cases of phthisis is obviously futile and entirely unjustifiable. In early and favorable cases of pulmonary tuberculosis the propriety of operation for intestinal tuberculosis is, to say the least, questionable, so long as we have no methods at our disposal to determine definitely the location of the lesions. It must be kept in mind that, even with small and early ulcers, strictly localized to a small segment of the intestine, other portions of the tract may be involved with tubercles.

The application of ultraviolet rays has been given an extensive trial at Montefiore Hospital and has been discarded because it has proved of no value whatever as a palliative measure.

SUMMARY

Tuberculous ulceration of the intestines occurrs in from 60 to 90 per cent of cases of lethal phthisis.

In over 75 per cent more than one subdivision of the tract and in 80 per cent the small and the large intestine were found to be involved.

The lower ileum and the cecum were the regions of the earliest localization of the tuberculous process in the great majority of cases.

Completely healing intestinal ulcers were rarely found at autopsy. Scars suggesting healed ulcers, with active lesions in the same or other portions of the tract, were more frequent. A tendency to healing in advanced and widespread disease was quite common.

In spite of the large number of advanced ulcers found in most cases perforation of the serosa was infrequent.

In the majority of cases the intestinal disease ran a completely latent course, irrespective of the extent or severity of the ulceration.

The presence of the complication cannot therefore be excluded because of the absence of symptoms.

There is no symptom or group of symptoms pathognomonic of tuberculous enteritis.

In a certain proportion of cases the intestinal complication is associated with diarrhea or diarrhea alternating with constipation, colicky pain, tenderness to palpation of the abdomen, blood in the stools and the signs of enteroperitonitis.

Diarrhea is not necessarily a symptom of advanced disease of the intestine. It occurs in cases with few and early lesions localized to a small area.

Severe, persistent and uncontrollable diarrhea, occurring in the course of advanced phthisis, practically always indicates the presence of intestinal ulceration. The more of the above symptoms are associated the more probable this complication.

None of the symptoms, occurring either singly or in combination, has any value whatever in definitely indicating which region or regions of the intestinal tract are involved. In the majority of cases disease of the small and large intestines must be assumed.

The cause of diarrhea and colicky pain and other symptoms in some cases and of their absence in other cases presenting a similar pathological picture is not definitely known. It appears that the location and depth of the lesions have little to do with the symptomatology. It is

probable that toxemia, amyloidosis and catarrhal conditions of the mucous membrane play an important rôle.

The value of the roentgen ray in the diagnosis of tuberculous ulceration of the intestine and particularly of early lesions and in disease of the small intestine still remains to be determined.

Operative interference, especially in advanced pulmonary tuberculosis, does not appear to be justifiable.

There is no scientific clinical and experimental evidence to show that ultraviolet rays have any palliative or curative effect on intestinal ulceration.

Calcium chloride appears to have some value as a palliative measure in some cases.

The prognosis of tuberculous ulceration of the intestine in advanced phthisis is invariably bad, and the onset of this complication ushers in the termination of the case within from three to six months.

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ASSOCIATED DISEASES IN PULMONARY TUBERCULOSIS[1]

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There is a tendency on the part of many medical men to conclude the search at the first definite signs of a disease and there let the diagnosis rest. Too infrequently do they continue until all other possible diseases are eliminated, unless obvious signs of an associated disease are present. It is true that many associated diseases, even if demonstrated, would not alter the course of treatment. On the other hand, there are associated diseases that really play the dominant rôle in producing pathological changes and symptoms. This point may be illustrated by a recent report by Reed and Wyckoff (1), according to which a patient had eight different diseases at one time, including gonorrhea, syphilis, otitis media, amebiasis, malaria and several forms of intestinal parasites. There are many such instances, possibly not so exaggerated as the one given, but in which a complete chemical, microscopic and serological study of body fluids and a neurological, psychiatric and pathologic-physiological examination will reveal a surprising number of unsuspected conditions. To verify this statement one has only to compare clinical with anatomic diagnoses after autopsy. Cabot (2) very aptly illustrated this point when he stated that 47 per cent of all his clinical diagnoses, checked by 1000 autopsies, were partially or wholly wrong.

The same conditions prevail in tuberculosis; not any more so than in other specialties and perhaps not so much so. Every specialist has a tendency to emphasize conditions that lie within his particular field and to slight those in others. This is quite natural, however, because he is more familiar with manifestations of disease in the specialty to which he has devoted most time. Granted this, there are altogether too many who seem to consider that the boundaries of the human body extend no further than the parietal pleura.

In arriving at a conclusion regarding an associated disease, it is therefore necessary to study the body as a whole as well as its special

[1] From the laboratories of the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

parts or organs. The various steps of summoning witnesses and taking evidence, selecting and rejecting testimony and rendering the final verdict, much the same as with a court, in convicting a criminal, are essential. The various clinical, laboratory and X-ray signs are witnesses, and nothing more than witnesses, that give the evidence while the physician must be the judge and the jury; judge, because he must assemble the evidence and correlate facts, and the jury, because he must render the verdict. A laboratory or clinical sign can no more make a diagnosis than can a witness render a verdict.

Before entering on a study of associated diseases in tuberculosis, it will be convenient to form some classification for a working basis. First, there are the patients who are not tuberculous, but whose symptoms more or less simulate tuberculosis. This group must be ruled out, a process which constitutes the chief problem in diagnosis. Then there is a second group which may be called uncomplicated tuberculosis. If there are any complications, they are due to the tubercle bacillus or its toxins. A third group is one with diseases due to secondary microörganisms in primary tuberculous infection, or the toxins of the secondary invader. The fourth group is of the type where the concomitant disease is independent of tuberculosis. This is the next hardest problem for the diagnostician in tuberculosis. These four types will be taken up in order.

Previous to the world war, the chief aim of the physician was to make a diagnosis of tuberculosis early. This practice had the effect of saving many people from far advanced disease. It also placed on the list of the tuberculous many people who did not belong there. The usual sanatorium treatment, however, will do little harm, but a great deal of good, to any suspect. Even though a number went through life with the idea that they had a limit of endurance due to such a disease it would do no harm. I believe that it was Oliver Wendell Holmes who stated, in substance, that a chronic disease in youth is a blessing, because the patient always takes better care of himself than he otherwise would.

On the other hand, there are disadvantages in needless forced inactivity. It is an economic loss to have a man idle for a long period when appropriate treatment would restore him shortly from another ailment. More, it practically revolutionizes a man's whole scheme of life and frequently causes him great expense and loss. Furthermore, it is the cause of much mental anguish to the patient, especially if information is not given in the most intelligent manner. There is nothing

more pernicious than scaring people about a disease that they look upon as death itself. If the physician can keep the confidence of his patient and see that proper treatment is given while under observation, it is better to reserve judgment until diagnosis is certain. This does not mean that he is to keep the patient in ignorance of the disease when diagnosis has been established. Such a practice is an ugly phase of medicine that should be a thing of the past.

It is safe to say that for the many who are correctly diagnosed as tuberculous only the occasional patient is mistakenly treated. Therefore, there is a preponderance of argument in favor of the policy of the past, even though many errors were made. But the next question is, why follow a partially erroneous policy, even though it does more good than harm, if the truth is available? Such truth is now being sought, and, as Stewart (3) has happily said, we are now striving for accuracy as well as early diagnosis. Accuracy of diagnosis, however, is not always possible, even with modern methods. There is always the doubt that an occult tuberculous lesion may be present. At any event, when all available evidence has given incontrovertible testimony in favor of tuberculosis, we must close the first chapter in diagnosis and turn to the next.

The second group, or the class including the uncomplicated cases of tuberculosis, will be passed over without comment for obvious reasons.

The third group includes the secondary infections in tuberculosis, that start from a previous tuberculous infection or come on as "camp followers" and eventually cause symptoms that are of varying grades of severity. Such conditions are infections in tuberculous cavities, pyogenic empyema, laryngitis, bronchitis, bronchiectasis, pleuritis, etc., which are due to secondary bacteria such as streptococci. It is true that such conditions as laryngitis, bronchitis, pleuritis, arthritis, hepatitis, etc., frequently accompany tuberculosis and are due solely to the tubercle bacillus or its toxins, but these conditions are all well understood and form only differential points from the associated conditions.

Last of all are those conditions that occur independently of tuberculosis, as collateral or concomitant disease, acting possibly as predisposing factors in tuberculosis or vice versa. This group will include most frequently the pneumonias, influenza, bronchitis, bronchiectasis, lung abscess, syphilis, empyema, gastrointestinal and genitourinary diseases, malnutrition, tonsillitis, endocarditis, pericarditis, osteomyelitis, etc. Certain conditions may fit into both classes three and four,

but even so there seems to be a sharp line of differentiation between the two groups. According to some such plan, associated diseases in tuberculosis may be studied systematically.

Tuberculosis *per se* may be responsible from 1 to 100 per cent of the symptoms of a disease. The bacilli may be present, even with only a very slight percentage of symptoms arising from them or their toxins. It is this type of patient that the author wishes to illustrate in this paper, that is, those in whom there is unquestionable tuberculosis present, yet overshadowed by other diseases or complications. At no time should one rest in "slothful overtrust," when tubercle bacilli are found, without eliminating other possibilities. There are two things to bear in mind constantly: one is to be careful about calling sputum negative cases tuberculous, and the other about calling sputum positive cases nothing but tuberculosis. The frank tuberculous cases, when found to be such, will cause no difficulty whatever in handling. It is the complications and associated diseases that arise that demand the greatest attention in tuberculosis work.

To illustrate this one special point, we are reporting three cases of tuberculosis, in which the concomitant diseases caused the dominant symptoms and the tuberculosis played a minor rôle,—far less so than surface appearances would indicate.

The first report is of a patient having unresolved influenza-pneumonia with a subsequent infection with Bacillus pyocyaneus and the development of active tuberculosis.

Case 1: S. L., female, 22 years, entered the institution, February, 1921, after having been pronounced tuberculous with no record of sputum examination. She had influenza in 1918 and had never felt well since. Sputum negative on admission and continued negative for three months. X-ray examination revealed heavy infiltration at bases of both lungs, rather dense hilum shadows, bronchial thickening, and relatively clear apices. There were profuse expectoration, 15 lbs. loss of weight and a daily afternoon temperature rise of 2°.

In April, 1922, the sputum was reported positive for tubercle bacilli and remained positive for three consecutive examinations. On close observation, however, there was a notable difference between the appearance of the bacilli and of those usually observed. They stained very faintly pink. Therefore, a guinea pig was inoculated and remained free from tuberculosis. The work was repeated and still results were negative; on a third attempt, however, the animal developed tuberculosis. Meanwhile, a microörganism was found that

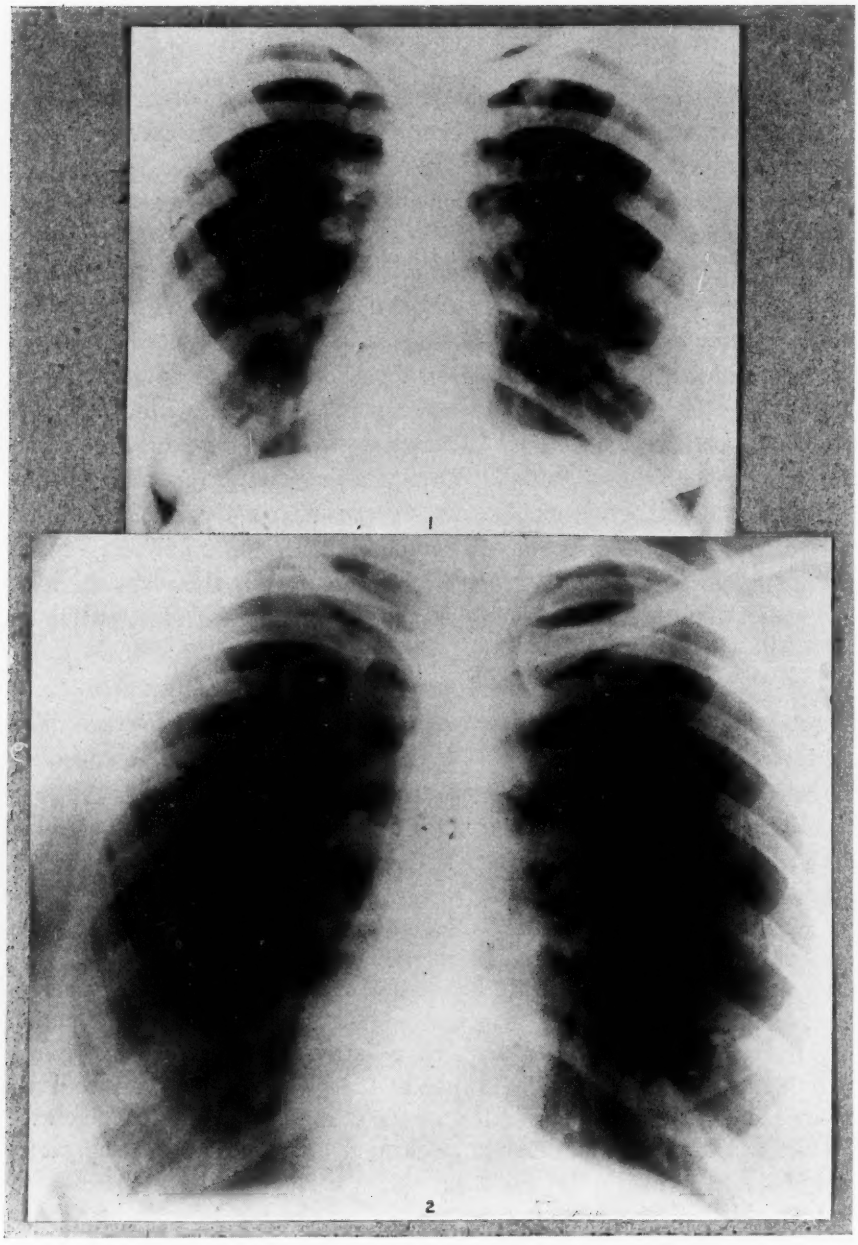

FIG. 1. X-RAY OF CASE 1 AT HEIGHT OF SYMPTOMS

Note marked bilateral basal infiltration and very slight infiltration toward right apex

FIG. 2. X-RAY OF CASE 1, SIX MONTHS AFTER FIG. 1, AFTER ALL SYMPTOMS EXCEPT EXPECTORATION HAD DISAPPEARED

The only change is a slight clearing of bronchial lymph node shadows and of infiltration toward right apex.

responded in every test to that of Bacillus pyocyaneus. This might have been anticipated earlier, because the sputum on standing would develop a green film, which would color the whole sample on shaking. The bacillus that retained a slight pink color was therefore Bacillus pyocyaneus. On thorough decolorizing no color of red remained. The question was raised, however, whether or not the patient had tuberculosis at all, or whether the positive sputum examinations were due to this faintly acid-fast bacillus alone.

When the third animal developed tuberculosis, however, the question was definitely settled that tuberculosis was present eight months after admission, but no information was gained regarding the earlier months. An X-ray examination at this time (fig. 1) revealed slight but definite infiltration from the hilum to the right apex.

A vaccine was prepared from the isolated pyocyaneus bacilli and a course of injections given, beginning with 100 million and gradually increasing the dosage. Almost immediately the patient began to show improvement, symptoms disappeared, and the patient gained weight and appeared to be on the road to recovery. Unfortunately, the type of pathological change present permitted of only limited improvement.

Our pathological findings in this type of case indicate a "rubbery" or "soggy" lung, resembling a hypostatic condition. McCrudden (4) has described this condition under the name *postinfluenzal chronic pneumonitis*. The unresolved influenza-pneumonia eventually became a chronic process. No doubt, a fibrosis set in from a long-standing "carnified" condition of the lung and a bronchial dilatation accompanied the process. In fact, Corrigan's theory of the cause of bronchiectasis is based on this very fact, namely, a fibrosis of a lung adherent to chest wall, which on expansion stretches the unsupported bronchial wall. However this may be, all pathologists agree that there must be a preceding infection or weakening of the bronchial wall.

At all events, this patient has reached the stage of pulmonary cirrhosis with bronchiectasis, wherein complete recovery cannot be expected although a gradual improvement is now in progress. She is working daily and feeling well ,and has gained full weight, but her sputum is still profuse, although not laden with so many pyocyaneus bacilli and very few tubercle bacilli. In fact, only one guinea pig has been positive since August, 1922. Her temperature is normal.

A recent X-ray of her chest reveals the same involvement at the base, with a slight diminution of the hilum shadows and possibly a thinning of the apical infiltration (fig. 2).

Case 2: E. G., a colored boy of 14 years, was admitted in November, 1921, with a diagnosis of far advanced pulmonary tuberculosis. In May, 1921, he had a tonsillectomy, following which he complained of pains in the chest,

night sweats, and loss of weight. The sputum was negative, but X-ray revealed a density of the lower border of the right upper lobe, which might have been an abscess. A subsequent examination showed a diffuse shadow over the whole right lung, becoming very dense at the base. The left lung was also infiltrated, chiefly in the lower lobe.

Unfortunately, no other radioscopic examinations were obtained. Sputum examination was repeatedly negative. No pleural fluid was obtainable on puncture. The clinical diagnosis was far advanced tuberculosis. The patient died in November, 1922. At autopsy there was found a marked bronchiectasis throughout the whole right lung, with many abscesses in the bronchiectatic cavities. A rather large abscess was found in the region between the upper

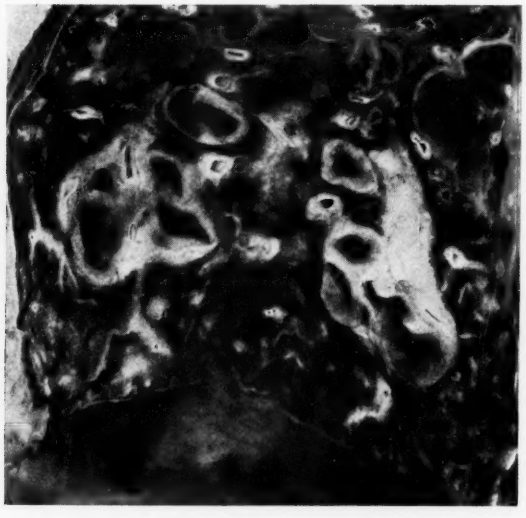

FIG. 3. CROSS SECTION OF LEFT LOWER LOBE OF CASE 2, SHOWING MARKED GENERALIZED BRONCHIECTASIS

and lower lobes in the midaxillary line on the right. The pleural cavity contained about a half-litre of cheesy pus. The left lung had a rather normal-appearing upper lobe and a marked bronchiectatic involvement of the lower lobe (fig. 3). There was marked hypertrophic pulmonary osteoarthropathy. The anatomic diagnosis was nonspecific lung abscess, bronchiectasis, etc., which was confirmed by competent pathologists. Hemolytic streptococci and Vincent's spirilla were found. The surprising fact was that on microscopic sections of the abscess cavity there were found many giant cells and much evidence of tuberculosis. Animal inoculation was also positive for tubercle bacilli.

Case 3: E. P., male, 40 years, was admitted to the institution as a moderately advanced case of tuberculosis. There was nothing unusual in the history. After admission, tubercle bacilli were found in the sputum. However, the patient began to fail rapidly, and a small tumor appeared at the right of the sternum, which on section was found to be a round-cell sarcoma. Prior to this there was nothing that would prevent a diagnosis of tuberculous adenitis of the lymph nodes of the mediastinum, except possibly the rather rapid course of the disease.

At autopsy a primary lymphosarcoma of the thymus gland was found, with metastases to the lymph nodes and liver, and direct extension to all adjacent tissues. On detailed microscopic study the tumor was found to be thymoma or a sarcoma of the reticular cells of the thymus, which is similar clinically but different histologically from a lymphosarcoma.

This report could extend over many cases that have come to autopsy in this institution. The conditions vary in quality and degree only. As an example: we have had three cases of ulcer of the stomach, one possibly tuberculous, which was not suspected before death, the other two of which were found clinically. We have found one case of chronic pancreatitis with diabetes; a case of hypernephroma at first diagnosed as tuberculosis because of metastatic growths in the lung (later the diagnosis was changed when the X-ray revealed the tumors in the lung); a case of tuberculosis having enteritis and a fistula from a ruptured appendix into the peritoneum and a valve-like fistula into the bladder producing a puzzling variety of symptoms and findings. Several interesting specimens of pneumokoniosis, a bronchogenic carcinoma and other equally interesting findings have come under our observation.

DISCUSSION

These three cases have been selected more or less at random from the clinical and postmortem records of this institution to illustrate as clearly as possible the importance and frequency of associated conditions in tuberculosis. These conditions have all been rather extreme, that is, the tuberculosis has played a very small part in any one of the cases reported.

The majority of patients who had had concomitant diseases have had more tuberculosis and less of the associated condition than the patients listed above. In any case, however, the importance of recognizing the true condition early is paramount in successful treatment.

The three cases reported here have been chosen to illustrate at least three great groups of cases that frequently produce difficulty in diagnosis and what may be called the "evaluation" of the respective pathological processes.

The first case, primarily representing influenza, also illustrates various other "by-products," such as bronchiectasis, and chronic interstitial pneumonia. Uncomplicated influenza in many instances caused not a little difficulty for clinicians and X-ray men, but, after it has been established that both influenza and tuberculosis play a part, the most difficult task is the evaluation of the respective rôles.

At this time, influenza and its relation to tuberculosis will be dealt with no further than a very brief mention of recent reports. It will require more time before a final balancing of accounts can be made as to the relation of the two diseases. Authorities differ and statistics are more or less misleading. In the short time that has elapsed since the epidemic, it seems that the longer we wait the more we perceive that influenza has played an important rôle in the spread of tuberculosis. Sloan (5) collected statistics from 29 tuberculosis institutions from October 1, 1918, to October 1, 1919, and found that 12 per cent of the patients had no signs of tuberculosis until after an attack of influenza. Heise (6) reported 10 per cent attributable to influenza in the Trudeau Sanatorium in the same period. Fishberg (7) immediately after the epidemic reported that he had seen no etiological effects of influenza. Since 1919 the toll seems to be increasing. Many patients complain that they have never "felt well since having the flu," although it may be two or three years after the epidemic. Douglas and Brown (8) report that 27 per cent of 615 patients of tuberculosis admitted to the Ohio State Sanatorium since 1919 had no signs of tuberculosis prior to the influenza epidemic of 1918. Klein (9) more recently states that influenza played a part in 39 per cent of tuberculosis cases, and that tuberculosis itself furnished no immunity against influenza; on the other hand, the tuberculous condition was aggravated by influenza.

At variance with these reports, Boards of Health from all over the country report a marked drop in mortality from tuberculosis. The explanation of this apparent disagreement is not so difficult as might at first appear. There were no doubt many weak individuals, potentially tuberculous, who died in the epidemic. Whether they were actively tuberculous at the time or not, the diagnosis was quite properly "influenza." Therefore, the crop of tuberculous deaths for a few subse-

quent years was thinned out by influenza. Again, there were many patients of influenza who had a subsequent tuberculosis that was called "unresolved influenza pneumonia," or something else, and not until the medical profession was able to differentiate the two, or until the sputum became positive, were the proper diagnoses made. More important than this was the effect of previous teaching and propaganda directed against tuberculosis. It was only a continuation of the general decline and was exaggerated slightly by the reasons given above, and also by the fact that the death rate in tuberculosis fluctuates at times.

It is argued by some that the hardships of war should increase the incidence of tuberculosis. This point has no doubt been overestimated. No doubt the soldiers who suffered exposure did have an increased incidence but the general conditions amongst the working classes were better than they ever were, except in Central Europe where there was not enough food (10). Even though the work was harder, and meat and bread allowances were cut, a sufficiently balanced ration was obtainable by all, and it was the first time, possibly, that the poorer classes as a whole did have sufficient food. Then the thrift engendered by the war, the increase of outdoor work, the precautions used in shop work to protect the workmen, and the restricted use of alcoholic drinks would tend to counterbalance the strain and disagreeable work placed upon a few. In addition, the people in general learned lessons from the draft boards, who found so many defective and tuberculous men, so that the average individual kept a closer watch on his health. This was particularly true in and following the influenza epidemic. Every one was more cautious than usual, and much less dissipation was manifest. The argument, therefore, that the war caused any great increase in tuberculosis incidence is not wholly valid. On the contrary, it may have reduced the incidence of tuberculosis in countries where the people were not starved.

It is a fact, not to be ignored, that much tuberculosis is attributable directly to influenza. There is a significant percentage of people who would never be tuberculous were it not for an attack of influenza. Therefore, not only should the delayed resolution of influenza be kept constantly in mind, but, more especially, the relation of this condition to tuberculosis, whether the bacilli have been found or not.

Regarding the occurrence of Bacillus pyocyaneus, there are not a few who report its presence in pulmonary infections, particularly in tuberculous cavities. Cornet (11), in examining the bacterial flora of 80 tuberculous cavities, reported finding Streptococcus pyogenes,

Staphylococcus aureus and albus, pneumococcus, pyocyaneus and Micrococcus tetragenous, in the order named. He also states that other investigators, including Kitasato, Petruschky, C. Spengler, Schabad, and others, found streptococcus more frequently than pyocyaneus, Diplococcus pneumoniae, staphylococcus, and Bacillus influenzae, in the order named. Reports are meagre, however, of cases in which it has been one of the dominant factors in causing symptoms, as was apparently true in the case reported.

An important question arises regarding the treatment of such a patient. The method of choice in treating chronic interstitial pneumonia of this nature, free from empyema, is by stimulation and exercise of the affected organ, quite the contrary of the accepted treatment for tuberculosis. The lethargic or toxic cells, that have been living in a vicious circle, between an impaired circulation and lessened vitality, need to be whipped into action. The circulation must be reëstablished, so that the poisoned cells may discharge the toxic products and receive nourishment to restore normal function. Elimination must be assisted where possible. When tuberculosis is present, however, this disease must be controlled first and continually watched, while treatment of the other is in progress, even at the expense of more lung fibrosis.

The second case illustrates, primarily, the group of pulmonary conditions arising from nonspecific abscesses, in the presence of a tuberculous focus that may or may not be stirred into full activity. Secondarily, it is an excellent illustration of the development and progress of bronchiectasis.

There are many valuable points to be learned from this case. First of all, the clinicians who were well grounded in tuberculosis made the diagnosis on certain physical signs only, whereas they should have considered the history of tonsillectomy, the X-ray examination and the absence of tubercle bacilli in the sputum, especially in the advanced stages of the disease. Had tubercle bacilli been found, and they would have been found, no doubt, if continued search had been made in the pleural fluid, nothing could have ever convinced the clinicians that tuberculosis played only an insignificant, if any, rôle in this patient's illness, as was actually the case.

On the other hand, pathologists, as well as clinicians, must bear in mind that there may be a mixed infection in any abscess; that tuberculosis may be present in nonspecific abscesses; that it may begin at any time during a nonspecific infection; and that it may cause few or all symptoms

and pathological findings of any mixed process, with all grades between the two extremes.

Incidentally, there are a few other conditions present which may be of interest to the surgeon as well as the physician. The liability of abscess following tonsillectomy from aspiration of septic material should be borne in mind, as pointed out by Davis (12), as well as some cases of bronchiectasis from this cause.

The last case illustrates lymphatic involvements that simulate, in a general way, tuberculosis, in cases of unquestionable tuberculosis. Adenomas, leukemias, Hodgkin's granulomas, and lymphosarcomas are a few of the conditions that come under this heading.

The interesting point in this case is that the tuberculous involvement was very slight. Only a few small caseous and calcified tubercles and one small cavity, less than a centimetre in diameter, could be found in the right apex. The tuberculous involvement was considered too slight to even cause a positive sputum from pathological examination alone.

Here is another instance in which the tuberculosis was only an insignificant factor. Its only importance was its ability to mask the graver condition.

SUMMARY

A general discussion on associated diseases in tuberculosis has been given and a brief classification on a pathological and etiological basis has been outlined. Emphasis is laid upon the point that sputum-negative cases should be diagnosed as tuberculosis with a great deal of care. On the contrary, the same care should be used in calling sputum-positive cases nothing but tuberculosis, for tuberculosis may cause few or all the symptoms. It is a problem therefore of correct evaluation of the symptoms of the various concomitant diseases, and on this evaluation to base the proper treatment. Cases have been reported from the clinical and postmortem records of the institution to illustrate the various points mentioned.

The author wishes to express appreciation to Dr. Irene Barber for the X-ray pictures and to Mr. Edward Weiss for the photographic work.

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A SYNDROME SIMULATING PULMONARY TUBERCULOSIS[1]

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Within the past few months there have come under our care three persons either with diagnosis of tuberculosis made elsewhere or presenting the usual symptoms of this disease, whose true condition has been found to be a combination of mitral stenosis and hyperthyroidism. They had fever, cough, hemoptysis, rapid pulse, loss of strength and (except in case 2) loss of weight. In each case prolonged and accurate study was necessary to arrive at a sound diagnosis.

Case 1: Was a professional man, educated, alert and intelligent. Both parents were living and well, as were also five brothers and two sisters. Two brothers were dead. One suffered a crushing injury to his chest, which was followed by empyema for which he was operated upon. Tuberculosis ensued and was rapidly fatal. The patient was at home with this brother for two months but sanatorium precautions were carefully observed. The other brother died of an unknown chronic disease, which did not resemble tuberculosis but rather the patient's own condition. The patient's wife died from embolism following operative delivery. Her previous health had been good. Their two children were both living and well.

The patient had measles and whooping cough in childhood. Both were mild attacks with prompt recovery and no sequellae. Two or three years ago he had mumps, and in 1918 a very mild attack of influenza. He had never been subject to colds or tonsillitis; neither had he undergone any surgical operations. There was no history of pneumonia, typhoid fever or malaria.

In November, 1920, without any warning, he spat up several mouthfuls of pure blood, unmixed with sputum. This incident recurred several times within the next three or four days. He did not feel ill, had no cough preceding the hemorrhage, and did not feel sick afterward. He remained in bed for a few days for fear of further bleeding and during that time spat up clots but no fresh blood.

[1] Read before the Bernalillo County Medical Society at Albuquerque, New Mexico, February 14, 1923.

Until March, 1921, he remained in fairly good health, entirely free from cough and sputum. At this time he had his second hemorrhage, spitting up one or two mouthfuls of fresh blood on two or three different occasions. He did not feel ill, nor was he incapacitated after the bleeding. The next month he raised a little blood-streaked sputum. After this he was free from all symptoms until March, 1922, when he again raised fresh blood in about the same amount as before. For the first time, during the winter of 1921–1922, he developed a morning cough and brought up mucus, which seemed to him to come from the larynx: there was no blood mixed with this sputum at any time previous to March, 1922. During all this time the patient was not more than five to seven pounds below his usual weight. Gradually, after November, 1920, other symptoms came on, such as extreme nervousness, insomnia, very rapid pulse on exertion or excitement, and gas in the stomach and bowels. Skilful internists, after physical and roentgenological examinations of the chest and gastrointestinal tract, made a tentative diagnosis of pulmonary tuberculosis and sent him to the Southwest.

When we examined him, neither repeated physical examinations nor roentgenograms revealed any evidence of active pulmonary tuberculosis. Persistent search failed to demonstrate tubercle bacilli in his sputum. Abdominal examination was entirely negative, as were also Wassermann and urine examinations. The faucial tonsils were injected and reddened but not enlarged. The larynx was normal. There was a fine tremor of the hands; the eyes were prominent, and the patient nervous and "jumpy." His height was 69 inches, and his weight, stripped, 121 pounds. Cardiac examination revealed the right border of the heart 1.5 cm. to the right of the sternal margin. Over the mitral area there was a very slight presystolic murmur, not transmitted and accompanied by no perceptible thrill. Six drops of adrenalin (1 to 1000) administered hypodermically brought out a rough murmur over the mitral area, beginning just before systole and continuing throughout the first sound. This murmur was not transmitted and there was no thrill. His basal metabolic rate was found to be 35 per cent above normal. Roentgen ray therapy was advised and has been systematically carried out.

At present the patient feels well, has no insomnia or gastrointestinal symptoms, is much less nervous, has a good appetite and has gained several pounds in weight.

Case 2: The patient was a girl aged 16. Family history was unimportant, except for one older sister who has moderately advanced pulmonary tuberculosis. The patient had spent only a few weeks with this sister and sanatorium precautions had been observed. She was robust in appearance and stated that she had never had a serious illness of any kind. Her sister informed us that she had always been nervous and hard to control, and that she was subject to violent fits of temper and was generally somewhat wayward.

During the summer of 1922, without premonitory symptoms and while walking along the street, she had a pulmonary hemorrhage. The amount of blood lost could not be accurately measured, but it amounted to several ounces. Immediately following this occurrence, bubbling râles were to be heard over the right upper, but within two days these had all disappeared and physical examination of her lungs was entirely negative. Over the mitral area, however, could be heard a soft, presystolic murmur accompanied by a slight thrill but not transmitted. The right heart extended 1 cm. past the right sternal border. She was found to be 62¾ inches tall and to weigh 111 pounds, stripped. These figures correspond closely to the normal for her age. However, her basal metabolic rate proved to be plus 60. All other physical examinations were negative, as were all other laboratory tests.

Shortly after this she returned to her home and we have heard no more of her. Our advice to her was X-ray therapy over the thyroid region and removal to a lower altitude for the cardiac condition.

Case 3: The patient was a nurse aged 32, intelligent and not at all neurasthenic. Her mother was alive and in good health at the age of 69. Her father died at that age, probably of a malignant tumor although the diagnosis at the time of death was uncertain. He had always had good health. There were five brothers and three sisters, all living and well. One great-uncle whom the patient never saw had tuberculosis. Otherwise the family history was entirely negative.

In childhood the patient had measles, chicken pox, mumps and whooping cough. All these diseases were mild with the exception of measles, and recovery from all was complete. She had never had pneumonia, scarlet fever, diphtheria or malaria. At the age of 19 she had typhoid fever and was very ill for three months, but had neither perforation nor hemorrhage and finally made a complete recovery.

She trained in Kansas City, graduating in 1915. At the completion of her course she was thin and overworked but, nevertheless, began work at once in city hospitals. During the summer of 1915 she began to cough, have an afternoon and evening temperature of 99° to 100° and raise blood-streaked sputum. She felt ill and weak. She was examined by competent medical men, none of whom were able to find definite evidences of lung disease. Her heart was also examined and pronounced normal. No roentgenograms of the chest were made. Despite her cough, fever and bloody expectoration she continued her work regularly.

In January, 1917, she went to Texas. While there (in March, 1917) she had her first hemorrhage, amounting to 2 or 3 ounces. For a day or two following she spat up clots. During this time she continued her work. In May, 1917, she returned to her home in Arkansas, where she remained until the

ensuing September. During this interval she continued to run her usual fever and failed to gain any weight, but raised no blood.

In September, 1917, she came to New Mexico and spent ten months in bed under a physician's care. During this time she raised no blood at all. Her physical examinations by various medical men throughout this period always showed intensified breath sounds and a few dry râles over the left base, with vagrant râles in various other portions of the chest. No tubercle bacilli were ever found in her sputum. After ten months of "chasing the cure" she resumed her professional work. At intervals since then she has had blood-streaked sputum and occasionally a little fever. There were always a little cough and mucoid expectoration.

Early in 1922 she removed to an altitude of about 7000 feet, where she continued nursing. She had no hemoptysis until April, when she noted streaked sputum for a day or two. Immediately after this she began to have pulmonary hemorrhages. At first she would raise a mouthful or two of pure blood at a time, and later from a half to two ounces at once. Hemostatic serum, pituitrin and calcium preparations were given with no results. The bleeding lasted five weeks and then gradually abated. In May, 1922, she returned to Albuquerque and came under our observation.

At that time she was thin and pale and looked very ill. To our surprise the physical examination of her chest showed no signs whatever of active tuberculosis. A stereoroentgenogram revealed the usual enlarged hilum shadows and the right border of the heart 2 cm. to the right of the sternal margin. There was no destruction of pulmonary tissue. Her hemoglobin was 85, Wassermann negative, and tuberculosis complement-fixation test negative. The pulse was 72, regular, and of good quality and force. No cardiac irregularities or murmurs were noted. The blood pressure was 112–70.

The Goetsch test was done, with sudden reaction after more than thirty minutes delay. Her pulse rose from 72 to 102, and her blood pressure from 112–70 to 132–60. Her face was deeply flushed, and there were very marked nervousness and pronounced muscular tremor. The cervical vessels throbbed visibly. Examination disclosed a harsh, presystolic murmur over the apex, mitral and tricuspid areas, not transmitted into the axilla but accompanied by a definite thrill.

Careful reëxamination after this showed that the cardiac dulness extended 2 cm. to the right of the sternum, that the apex beat was located in the fifth interspace 2 cm. medial to the midclavicular line, and that there was a slight impairment of resonance over the left upper lobe anteriorly. We also noted at this time a slight cyanosis of the finger tips, and, upon questioning the patient closely, learned that she herself had at times noticed a cyanosis, not only of the fingers, but also of the lips and face. She also admitted some dyspnea upon unusual exertion or climbing. Fluoroscopy done upon this day con-

firmed the enlargement of the right heart. A few days later a control test for the Goetsch test was done. It was entirely negative. Many cardiac examinations were made at later intervals. These usually showed a soft presystolic murmur over the mitral area only.

After some discussion an estimation of her basal metabolic rate was made, with a result of plus 24. Following this, X-ray therapy was instituted. After eight treatments the patient was obliged to resume work. Throughout the summer she handled a very difficult position. In spite of this she gained several pounds, and at the present writing feels very well, has no fever, sleeps well and has very few nervous symptoms. Her basal metabolic rate is now within normal limits. She had a hacking cough with a little mucoid expectoration but has had bloody sputum only twice since May. Removal to a lower altitude has been advised on account of the cardiac lesion.

We have had another case in which the combination of mitral stenosis and hyperthyroidism played an important rôle. This patient was a young man 25 years old. For three years past he had, at varying intervals, pulmonary hemorrhages without prodromal symptoms and without sequellae. During all this time he had a slight morning cough with mucoid sputum. A significant feature was his persistent failure to gain weight between hemorrhages, when entirely free from symptoms. In the summer of 1922 a diagnosis of pulmonary tuberculosis was made and he was sent to the Southwest. To the casual eye he presented an appearance suggestive of hyperthyroidism such as quick, nervous movements, prominent eyes and marked general irritability. Careful study finally established a diagnosis of early pulmonary tuberculosis without caseation or cavitation, complicated by a marked mitral stenosis and moderate hyperthyroidism (basal metabolism plus 30). Roentgen ray therapy resulted very promptly in a gain of several pounds, a marked diminution of his nervous symptoms and a much less rapid pulse.

At present we have under observation a patient sent to us with a diagnosis of early pulmonary tuberculosis, in whom we have not so far been able to discover any positive evidence of active tuberculosis; on the contrary there are very definite signs and symptoms of both mitral stenosis and hyperthyroidism. The presystolic murmur and thrill are constantly present and the basal metabolic rate is plus 23. This young man is still beng studied and the outcome of our investigations will be reported at a future date.

SUMMARY

Mitral stenosis and hyperthyroidism, combined, may present a clinical picture simulating pulmonary tuberculosis; namely, loss of weight and strength, indigestion, cough, hemoptysis, actual hemorrhage from the lungs, low fever and rapid pulse.

Careful cardiac examination is necessary to establish the presence or absence of mitral stenosis. Small doses of adrenalin, hypodermically, will reinforce the murmur if one is present. Fluoroscopy may reveal enlargement of the right heart in these cases.

Estimations of the basal metabolic rate are required to corroborate the clinical symptoms in making a diagnosis of hyperthyroidism.

When this combination of cardiac and endocrine disorders complicates tuberculosis, treatment of the syndrome may do much to assist the patient in his struggle with the tuberculous infection.

A STUDY OF THE LIMITATION OF CHEST MOVEMENT, CHEST THICKNESS AND MUSCLE SPASM IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS AND THEIR RELATION TO PLEURISY[1]

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An opportunity offered itself to the writer during the past year to attempt to correlate the limitations of movement of the chest with physical and X-ray findings in a group of 200 apparently healthy persons and tuberculous patients at Trudeau Sanatorium. Clinical impression has held that the simpler methods of inspection and palpation give great, but usually little credited, aid in the diagnosis of early tuberculosis. The time-honored methods of sight and touch are often relied upon to confirm diagnoses made otherwise by newer and less simple means. No accounts can be found in the literature, however, which concretely attempted to evaluate these methods. No one, apparently, has attempted to check up the results of inspection and palpation with the more certain measures of diagnosis, such as the distribution of râles, the X-ray, etc. The clinician and the diagnostician, consequently, have been at a loss to evaluate the evidence they have accumulated by means of inspection and palpation. He frequently, and in fact probably quite generally, uses such evidence to bolster up the diagnosis; uses it as "clinical impression" in confirmation of this or that possible diagnosis; but he cannot use it as definite concrete proof, because he is not certain of its definite and concrete value. It was in an attempt to give such value to the evidence gathered by inspection and palpation, that this clinical study was undertaken.

Two hundred individuals, either patients or workers at the Trudeau Sanatorium, were studied. One hundred and sixty of these were tuberculous, being mostly minimal and moderately advanced, with some far advanced cases. The sexes were proportioned as follows: 84 females and

[1] This study was pursued, while the author was a Fellow at Trudeau Sanatorium, under the direction of Doctors Lawrason Brown and Fred H. Heise, whose help and stimulation are greatly appreciated by the writer.

116 males. The cases were studied to obtain data on five different points of interest:

1. The relationship existing between limitation of chest movement and lagging, and the side and amount of tuberculosis.
2. Correlation of muscle spasm with side and amount of tuberculosis.
3. Relation of thickness of chest to side and amount of tuberculosis.
4. Relation of chest movement to pleurisy.
5. Relation of chest movement and pleurisy to pleural movement at the bases (diaphragmatic excursion).

Other points, for example, supraclavicular and infraclavicular depressions, as studied by Bray, have been adequately reviewed and consequently were not again studied.

CHEST MOVEMENT

A difference in chest movement, whether actual limitation of motion of one side, or merely lagging, is one of the easiest of physical signs to elicit. Inspection, combined with palpation, enables one to detect very slight differences in movement of the chest. However, just to what extent lagging or limitation of chest movement can be relied upon to indicate pulmonary involvement, has been, as mentioned above, unknown. Accordingly, the greatest stress in these studies was laid upon the question of chest movement. If, after finding, by means of inspection and palpation, a definite difference in movement, one can be as definitely certain of pulmonary involvement on the restricted side, we have at once an easy, rapid and certain aid in physical diagnosis of the chest. Just to what extent such a sign is reliable, the following figures attempt to show.

It must first be mentioned that in practically every instance (97 per cent) in which a difference of chest movement was noted a lagging was also noted. The following figures for limitation of chest movement, therefore, correspond to the figures for lagging:

Of the 160 tuberculous cases, limitation of chest movement, on one side or another, was found in the entire number. Of the 40 nontuberculous controls 35 were free from limitation, while 5 showed limitation of chest movement. All of these 5 showed by X-ray a peritruncal mottling, but not in sufficient amount to warrant a diagnosis of clinical tuberculosis. One of these five had a troublesome chronic bronchitis of many years' standing. Of the 160 tuberculous cases showing limitation of chest

movement, the limitation was on the side containing the larger amount and older tuberculosis in 140 cases (87.5 per cent). In 20 (12.5 per cent) cases, the limitation was on the opposite side. In other words, diagnostically, limitation of chest movement can be relied upon to diagnose the side of the greater tuberculosis in 87.5 per cent of the cases with an error in 12.5 per cent. Interestingly enough, an analysis of the stage of the cases shows the following figures:

Of 23 Far Advanced cases limitation of chest movement and extent or greater extent of lesion correspond in 22 or 95.6 per cent; incorrect in 1 or 4.4 per cent.

Of 120 Moderately Advanced cases limitation of chest movement and extent or greater extent of lesion correspond in 109 or 90.8 per cent; incorrect in 11 or 9.2 per cent.

Of 17 Minimal cases limitation of chest movement and extent or greater extent of lesion correspond in 9 or 53.0 per cent; incorrect in 8 or 47 per cent.

Conclusions, if any, to be drawn from so small a series indicate that limitation of chest movement and lagging, as diagnostic aids in tuberculosis, are most reliable in far advanced cases (95.6 per cent), next in moderately advanced cases (90.8 per cent), and least reliable in minimal cases (53 per cent). It is pertinent to observe here that in far advanced cases, in which diagnostic aid is least needed, limitation of chest movement and lagging afford the greatest aid; whereas, in minimal tuberculosis, where diagnostic aid is most needed, limitation of chest movement and lagging afford the least aid.

MUSCLE SPASM

The determination of muscle spasm and muscle atrophy, as practised most conspicuously by Pottenger, was made in all cases. To ensure trustworthy technique, determinations were made in a large series not included in the figures. All earliest recorded determinations were repeated at least once or twice at subsequent intervals. Of the 160 tuberculous cases, muscle spasm, as an index of the side of tuberculosis (side of either the most recent or most active lesion), was correctly diagnosed in 92 cases (57.5 per cent). In 16 cases (10 per cent) we diagnosed incorrectly, and in 52 cases (32.5 per cent) we could elicit neither muscle spasm nor atrophy. Of the forty nontuberculous cases, muscle spasm was elicited in 4 instances, which would, considering the entire

series of 200 cases, bring the percentage of correct diagnoses to 64 per cent, incorrrect to 10 per cent, and the no-spasm group to 26 per cent. The figures for the stages of tuberculosis are much the same as those given above for chest movement:

Of 17 Minimal cases correct diagnosis in 8 or 47 per cent; incorrect, 6 or 35 per cent; no spasm, 3 or 18 per cent.

Of 120 Moderately Advanced cases correct diagnosis in 72 or 60 per cent; incorrect, 9 or 7.5 per cent; no spasm, 39 or 32.5 per cent.

Of 23 Far Advanced cases correct diagnosis in 12 or 52 per cent; incorrect, 1 or 4 per cent; no spasm, 10 or 44 per cent.

These figures seem to indicate that muscle spasm is least reliable in minimal cases, or in those in which diagnostic aid would be most helpful.

THICKNESS OF CHEST

A difference in the thickness of the chest has often been hailed as an aid in diagnosis of lung disease. Measurements by calipers, by the single or double tape, or by the eye, have succeeded one another, finally to be discarded, and wisely so, as our figures would indicate. The procedure followed by us was to measure the thickness of each chest with calipers from the fifth costosternal junction to the spine of the vertebra posteriorly at a corresponding horizontal level. Any differences less than 0.5 cm. were disregarded. The limits of error of the method are great, owing to the inherent variation of the shape of the chest, the state of nutrition of the patient and the age of the tuberculous process. Of the 160 tuberculous cases, only 50 (31 per cent) showed a dimunition of chest thickness on the side of the older or greater tuberculous process; 35 (22 per cent) showed an increased thickness of the chest on this side; while 75 (47 per cent) showed no difference in the thickness of the chest. The analysis for the stages of tuberculosis is as follows:

Of 17 Minimal diminished thickness in 9 or 53 per cent; increased thickness in 2 or 12 per cent; no difference in 6 or 35 per cent.

Of 120 Moderately Advanced diminished thickness in 34 or 29 per cent; increased thickness in 26 or 21 per cent; no difference in 60 or 50 per cent.

Of 23 Far Advanced diminished thickness in 7 or 30 per cent; increased thickness in 7 or 30 per cent; no difference in 9 or 40 per cent.

One would expect to find, if in any group, a larger proportion of contracted chests among the far advanced tuberculous cases. Our figures, however, show a smaller proportion in this group than in the minimal

cases; 30 and 53 per cent, respectively, with chest walls diminished in thickness on the side of the greater and older tuberculosis. Such a finding might indicate that in minimal cases it would be worth while diagnostically. However, the fact that, in all types of cases, 47 per cent show no difference in chest measurement, immediately subtracts from the possible value of the finding. Measurements of chest thickness are of little aid.

PLEURISY AND CHEST MOVEMENT

The problem of the causation of the limitation of chest movement is an interesting one; that of correlation of such physical findings with the presence of pleurisy in the chest is equally interesting. We based our findings of pleurisy on those indications commonly accepted by the roentgenologist in stereoscopic plates, at the apex or base or both. Correlation of such X-ray findings of pleurisy with the limitation of chest movement found by inspection and palpation is as follows:

Of 160 tuberculous cases 80 (50 per cent) showed pleurisy on the same side as limitation of chest movement or lagging; 23 (14.3 per cent) showed pleurisy on the opposite side to that of limitation of chest movement, with no pleurisy on the limited side; while 57 cases (37.7 per cent) showed no pleurisy as discernible by X-ray, but all did show a limitation of movement.

The 80 cases showing a direct correlation of pleurisy to limitation of chest movement, that is, both being present on the same side, were further analyzed for the relationship of pleurisy, limited to either apex or base alone, to chest movement.

Of 61 cases showing pleurisy at either apex or base alone, the entire chest on that side was limited in movement in 33 (54 per cent). Of these 61 cases showing pleurisy at either apex or base alone, chest movement was limited at that apex or base alone in 19 cases (33 per cent).

The remaining 9 (13 per cent) were cases showing pleurisy at the base alone but having the chest limited in motion at the apex alone.

Of the 61 cases there were 37 which showed pleurisy at the apex alone. Of these 18 (49 per cent) showed limitation of chest movement at the apex alone and 19 (51 per cent) had the entire chest limited in movement.

The influence of pleurisy, as seen by the X-ray, can be summed up as follows: In a majority of cases of pulmonary tuberculosis there is a direct relation between limitation of chest movement and pleurisy. Pleurisy localized to either apex or base affects the entire chest wall by limiting movement throughout in a majority of the cases. Pleurisy

localized in the apex has a relatively greater power to so limit chest movement throughout than has pleurisy at the base.

PLEURAL MOVEMENT (DIAPHRAGMATIC EXCURSION)

A common chest finding by percussion at the bases posteriorly is the diaphragmatic excursion, more properly called pleural movement, since by such percussion excursion of the pleurae, rather than the diaphragm, is determined. This finding was secured in 148 of the tuberculous cases and the results were correlated with the presence of pleurisy at the base. Percussion differences of 0.5 cm. or less were disregarded and considered as normal.

Of the 148 tuberculous cases, 60 (41 per cent) showed a correspondence between limitation of pleural movement and limitation of chest movement, that is, both occurred on the same side; 31 cases (21 per cent) showed no correspondence, that is, chest movement was limited on the side opposite to that which showed limitation of pleural movement; and 56 cases (38 per cent) showed no difference in pleural movement, although all showed a limitation of chest movement on one side or the other.

In regard to the relationship between differences in pleural movement and the presence of pleurisy at the base, as seen by X-ray, the following figures are of interest: Out of 148 tuberculous cases, 50 (34 per cent) showed a correspondence between limitation of pleural movement and X-ray, that is, the side of lessened pleural movement and basal pleurisy was the same; 19 cases (13 per cent) showed no such correspondence, the basal pleurisy in these being on the side opposite to that showing diminished pleural movement; and 79 (53 per cent) of the cases were lacking either in a difference of pleural movement or in basal pleurisy.

An analysis of the cases by stage of tuberculosis for the above points reveals virtually the same figures. Minimal, moderately advanced and far advanced tuberculosis act similarly, in so far as limitation of chest movement, pleural movement and basal pleurisy are concerned. As to the frequency of all of these findings on the same case, 19 out of the 148 cases (12.8 per cent) showed a correspondence between pleurisy at the base, diminution of pleural movement at that base and limitation of chest movement on that side.

SUMMARY AND CONCLUSIONS

A clinical study was undertaken to evaluate certain physical signs elicited by inspection and palpation, and to afford a standard by means of which the true worth of such signs as diagnostic aids in tuberculosis could

be established. The following points of interest were studied: 1. Relationship between limitation of chest movement (and lagging) and the side and amount of tuberculosis. 2. Correlation of muscle spasm to the side and amount of tuberculosis. 3. Relation of thickness of chest to side and amount of tuberculosis. 4. Relation of chest movement to pleurisy. 5. Relation of pleural movement (diaphragmatic excursion) to chest movement and to pleurisy.

1. Limitation of chest movement as an index of the side and amount of tuberculosis was found to be correct in 87.5 per cent of the series studied. Limitation of chest movement is most reliable as a diagnostic sign in far advanced cases (95.6 per cent); next, in moderately advanced cases (90.8 per cent) and least reliable in minimal cases (53 per cent); a reliability which is in inverse ratio to the need of diagnostic aid in tuberculosis.

2. Muscle spasm was found to be an accurate diagnostic aid in 57.5 per cent of the cases, an incorrect aid in 10 per cent and absent in 32.5 per cent. As with limitation of chest movement, muscle spasm seems to be least reliable in minimal cases.

3. Diminution in thickness of the chest cannot be depended upon to indicate the side of involvement in tuberculosis. Thirty-one per cent of the cases showed such a diminution, 22 per cent showed an increase in thickness on the affected side and 47 per cent showed no difference whatever in chest thickness.

4. There is a direct relationship between limitation of chest movement and pleurisy, as seen by the X-ray, in just half of the cases of our series (50 per cent). Pleurisy localized to either apex or base alone affects the entire chest wall (rather than locally at the apex or base) by limiting motion throughout in a majority of the cases (54 per cent). Pleurisy localized in the apex has a relatively greater power to so limit chest movement than has pleurisy at the base.

5. Diminution of pleural movement (diaphragmatic excursion) and limitation of chest movement corresponded in side in 41 per cent of the cases, was different in 21 per cent and not different in 38 per cent. Diminution of pleural movement and basal pleurisy corresponded in side in 34 per cent of the cases, was different in 13 per cent, and either one or the other was lacking in 53 per cent. In only 12.8 per cent of 148 cases was there a definite correspondence between the three factors, that is, limitation of chest movement, diminution of pleural movement and basal pleurisy on the same side of the chest.

EXPERIMENTAL OBSERVATIONS ON INTRATRACHEAL AND INTRANASAL INJECTIONS IN RABBITS[1]

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Owing to the fact that numerous favorable reports have been made relative to the therapeutic value of carbonaceous material in tuberculosis, it is imperative that better methods of administration be devised, than heretofore, if any beneficial results are to be expected from their use. Various sporadic attempts have been made during the past century to treat pulmonary tuberculosis by the inhalation of finely divided particles, particularly coal dust, and quite recently the problem has been attacked with unusual vigor. We felt fully justified, therefore, in attempting to improve the methods of intrapulmonary therapy in the hope that some valuable results may ensue in this field of work.

In reviewing the literature we found that Beddoes was one of the first to use carbonaceous material in the treatment of tuberculosis and asthma. His reputed cures, however, appeared too fantastic to seem possible. Scudamore introduced an inhalation therapy, using tincture of iodine and other mixtures, administered in atomized state. Maddock, Fitch, DaCosta and many others accepted this therapeutic method, and all claimed beneficial results. Placing a rabbit in a finely-meshed sack, containing dust, and whirling the sack around in the air for fifteen to twenty minutes, Solis-Cohen demonstrated quantities of the dust in the animal's lungs at necropsy.

At the present time there seems to be a great deal of controversy as to whether men who work in coal mines are more susceptible to tuberculosis, or have a greater resistance to it. In a recent report Harrington and Lanza, who have examined the lungs of miners of Butte, Montana, are of the opinion that inhalation of dusts in mines "predisposes man to various infections of the lungs and bronchial passages" and that few victims of miners' phthisis escape subsequent infection. Ogle, Sommer-

[1] From the laboratories of the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

field and Hirt believed that men engaged in work associated with coal dust were somewhat immune to tuberculosis. Idel thought that porous coal dust absorbed the tubercle bacilli and rendered them inert. Klotz is of the opinion that the inhalation of coal dust produces somewhat of an immunity, which appears to depend upon the morphological characters of the dust particles. He further states that there is considerable difference between the coal miner's lungs and those of the city dweller. The particles inhaled by the coal miner are considerably larger and more angular. These factors no doubt predispose the subjects to so called miners' consumption. The angular particles act as irritants around which a good soil for tubercle bacilli is formed. However, it has been demonstrated by Papasotiriu that coal dust had no influence upon the growth of tubercle bacilli on glycerine agar cultures, and Cornet was unable to protect animals against air-borne tuberculosis by means of the inhalation of coal dust. Cesa-Bianchi, who exposed guinea pigs to coal dust, gypsum, talc, etc., found that these animals, when later injected with tubercle bacilli, showed marked cavity formation, while control animals, not receiving the dusts, showed little or no tuberculosis. Willis in a recent article states that the general unsanitary conditions in mines, plus the absence of light, etc., might account for the excess of tuberculosis among miners. We do not believe that this factor alone is the predominant cause.

On the other hand there are various favorable reports relative to the inhalation of soot or very finely divided carbon. Holman has pointed out that soot has a definite bactericidal action, on account of its content of phenols and acids, and that broth and other fluids, treated with soot, have conferred upon them a definite germicidal power. This demonstrates clearly that coal dust and soot are in no way similar in action. Furthermore, coal dust would have a tendency to act more like silicious particles, because of the similarity existing between grinders' and miners' phthisis. The inhalation of coal dust predisposes the body to infection with the tubercle bacillus by constant irritation, while soot, which is inhaled, is more finely divided and does not have the tendency to produce the same amount of irritation. Gye and Kettle have emphasized this point in a very emphatic manner: "It is established of course, that coal miners are more liable to pulmonary tuberculosis, than other members of the general population."

EXPERIMENTAL

Our work was roughly divided into two phases; first, the simplification of the technique of intrapulmonary inhalation and, second, the application of these methods. In general, we followed the plan previously described by Mullen and Ryder and by Corper and Robin. We have used many animals, chiefly rabbits; and, by adding a few technical procedures to the method first described by Mullen and Ryder, we have been successful in getting large quantities of suspended matter into the lungs, without the aid of an anesthetic.

Experiment 1: A rabbit was placed squarely on its back and about 3 cc. of india ink was allowed to flow slowly into one nostril. While the material was flowing, slight pressure was brought to bear at intervals on the abdomen, thereby forcing respiration. Half an hour after inhalation the animal was killed with ether and autopsied. Macroscopic examination failed to show any carbonaceous material in any of the lobes of the lungs or in the lymph nodes. Microscopic examination revealed a few pigment-laden cells, and some pigment in the tracheobronchial lymph nodes. Although Willis asserts that animals (guinea pigs) that have been kept in cages for over two years show spontaneous anthracosis, we believe that some of the material observed in the lymph nodes of this animal had been inspired.

Experiment 2: The same procedure was followed on another rabbit, except that the treatment was repeated on the two following days. Although it was observed that much of the material was swallowed, rhonchi were elicited over the entire chest. The animal was killed by the slow administration of ether twenty-four hours after the last inhalation. Necrospy showed extensive blackening of both lungs, chiefly in the dependent portions. Microscopic sections showed many pigmented cells, and considerable infiltration of phagocytic cells. None of the material was seen in the larger bronchi but many of the alveoli were almost filled.

Being convinced of the possibility of aspiration without the use of an anesthetic, we next attempted to find what value the postural effect of the animal during the inhalation period would have on the distribution of the material in the lungs. As in the method first described by Corper and Robin with the previously mentioned modifications, we were able to demonstrate that the material would flow into the lowermost part of the lung by the attraction of gravity.

Experiment 3: This was an exact repetition of experiment 2, except that the animal was held lying on its right side. The nose was elevated and the ink allowed to flow in. Macroscopic observations showed that all the carbon had

infiltrated into the right lung. Microscopically, no material was found in the left lung, while the right presented a similar appearance to the lungs of the animal used in experiment 2.

Experiment 4: This was a repetition of experiment 3 except that the animal was held on its left side. The results at necropsy and the microscopic findings were the same as in experiment 3, except that the conditions found in both lungs were reversed. No fibrosis was found in any of these sections.

We next attempted to follow the course of the ink in rabbits previously inoculated intravenously with virulent bovine tubercle bacilli. Three weeks after inoculation of the bacilli, the animals were given inhalations of suspended carbon (india ink) in the various postures previously described.

Experiment 5: This animal was held squarely on its back and given four successive aspirations, twenty-four hours apart, and finally killed three weeks after the last aspiration. Macroscopically, there were many tubercles scattered throughout the lungs, some surrounded by blackened rings. Microscopically, there were many typical tubercles, some almost completely surrounded by carbon pigment. There were many giant cells and considerable phagocytic cell infiltration. Some of these cells contained pigment granules. Occasionally, giant cells were found, containing pigment, some almost completely obliterated by the carbon.

Experiments 6 and 7: Experiments 6 and 7 were repetitions of experiment 5, with the animals held on the right and left sides, respectively. In each case unilateral infiltration of carbon was observed. The lungs which showed the carbonaceous deposit did not exhibit any difference in the tuberculous process from that in the carbon-free lungs.

The deposition and distribution of tubercle bacilli and india ink, when the ink was given first and the animals afterwards inoculated, differed in no way from the above mentioned experiments.

From these experiments it is evident that the results obtained were due to gravity or negative pressure produced by inspiration. To find which was the predominant factor we attempted postural experiments by tilting the animal and administering anesthesia. Our results showed that, after administering a soot-suspension to a lightly anesthetized rabbit, with head down on a table titled 30°, none of the material was found in the lungs at autopsy. If, however, deep anesthesia were administered, the prolonged inspiratory movement forced some material into the lungs. If the table was titled at 45° or completely inverted and deep anesthetic administered, no trace of carbon was found in the lungs.

One important observation that came to our attention during these experiments was that the animals, which received the suspension under

anesthesia as previously described, possessed a more localized blackening in the dependent portions of the lungs than those without anesthesia, yet there was by no means an even distribution in the latter. This made it imperative to devise some means of producing massive infiltration which would have more of an even distribution and, if possible, a method whereby an anesthetic would not be necessary. Eventually, a method was worked out whereby animals could be made to inhale the dust with air, by an insufflator. Employing this means, a more generalized distribution was obtained. Because of the fact that soot is reputed to have a germicidal power, it was thought that if quantities of it were given, an inhibition of the growth of the tubercle bacillus would result.

Experiment 8: A normal rabbit was held on its back and a paper cone, which fitted snugly, was placed over the nose. Into the hole at the apex of the cone a quantity of soot (made by burning gum camphor) was blown from a rubber bulb to which was connected a glass tube. Immediately after the soot was administered, the bulb was replaced by a similar empty one, and air was continually blown in to keep the particles in circulation. This treatment was kept up for ten minutes each day, for six consecutive days, and the animal was killed and autopsied forty-eight hours after the last inhalation. Macroscopically, much carbon infiltration was seen throughout both lungs, the distribution of which appeared to be even on all surfaces. Microscopic sections revealed much deposition of pigment. Many of the alveoli and lymph spaces were partially filled with carbon. There was much phagocytic cell infiltration.

Experiment 9: Five normal rabbits were injected intravenously with a virulent strain of bovine tubercle bacilli. Six hours later, each rabbit was taken through the insufflation procedure described in the previous experiment. After six insufflations one of the animals was killed six days later with ether. Macroscopically, there was much carbon infiltration scattered evenly throughout all lobes, but very little evidence of tuberculous infection. Microscopically, there was little evidence of tuberculosis. Carbon was found in the tissues around the bronchi and in the lymph spaces. There was comparatively little phagocytic cell infiltration. Many of the alveoli were filled with red blood cells.

Three days later one of the animals died. Macroscopically, the cause of death was determined to be pneumonia. Numerous early miliary tubercles were perceived, and much carbon infiltration at the lung periphery. Microscopically, early tubercles in the process of formation were scattered throughout. Pigment was found in, and partially circumscribing, some of the tubercles. It was also massed in the lymph spaces and lying free in some of the alveoli. Some phagocytic infiltration was observed. It was interesting to notice that, in the pneumonic part of the lung, it appeared as though the carbon

had been expelled from the tissues, and could be discerned lying free in many large bronchi. Some of the lymphatics, however, still retained the carbon.

Twenty days later another animal was killed and autopsied. Macroscopically, the lungs showed numerous miliary tubercles scattered evenly throughout, nearly all of them having rings of carbon encircling them. There was no pulmonary congestion or pleurisy. Microscopically, there was a picture similar to the nonpneumonic parts of the lungs of the previous animal, except that the tubercles were more advanced and appeared more completely encapsulated by rings of carbon. Much carbon was found in the tubercles.

The remaining animals were given four more insufflations, and killed six weeks afterward. All were similar to those previously described in the early part of the experiment, except that there was more infiltration of carbon and more advanced tuberculosis.

DISCUSSION

From this series of experiments we are able to deduct some interesting observations. Although soot may be bactericidal *in vitro*, it does not appear to inhibit the growth of tubercle bacilli when inhaled into the lungs. As has been described by Haythorn, Foot, and others, the particles seem to be taken up by the same type of cell as in the tubercle bacillus, that is, the phagocytic cell, having its origin in the endothelium of the capillaries. These cells are then deposited in and around the tubercle. When foreign particles find their way into the lungs, many of these cells (which are in proportion to the amount of foreign substance) seem to be liberated, and act as phagocytes. This theory, however, has not yet been universally accepted.

In observing the animals treated with carbon, we noticed that they became more susceptible to pneumonia than the normal animals. Haythorn states that anthracosis, or any process interfering with the lymph drainage, is a factor in causing delayed resolution in pneumonia. In none of our experiments reported here have we noticed any fibrosis.

While our experiments have been completely negative as to the treatment of tuberculosis with soot and carbon (india ink), we are of the opinion that possibly some advantages might be obtained with this method of intrapulmonary therapy, should there be found a suitable tuberculocidal agent that may be administered directly into the lungs.

Clinically, it has been repeatedly noticed that lung abscess, bronchiectasis, and aspiration pneumonia frequently follow tonsillectomy, or other nose and throat operations, an observation which has been studied bacteriologically by Davis and others. Of the causative factors that may produce this condition, possibly the depth of anesthesia (ether) and the posture of the patient play very important rôles.

SUMMARY

We have been able to produce massive infiltration by the aspiration of carbon (india ink) without the aid of an anesthetic. The material aspirated in this manner tends to gravitate to the dependent portions of the lungs.

Dry soot, when insufflated, produces a uniform anthracosis throughout both lungs.

When soot is inhaled, it tends to encapsulate the tubercle, but apparently does not inhibit the growth of tubercle bacilli in the lungs.

No fibrosis was observed in the lungs of any of the animals in a period as long as ten weeks.

When light anesthesia is given to an animal lying head down, on a board tilted at 30°, no carbon is aspirated, but in deep anesthesia much carbon is found in the lungs.

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Fig. 1

Fig. 2

Fig. 3

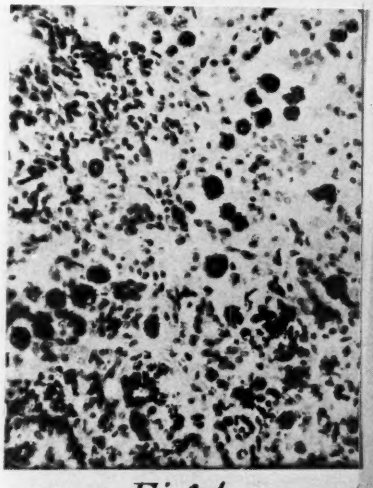

Fig 4

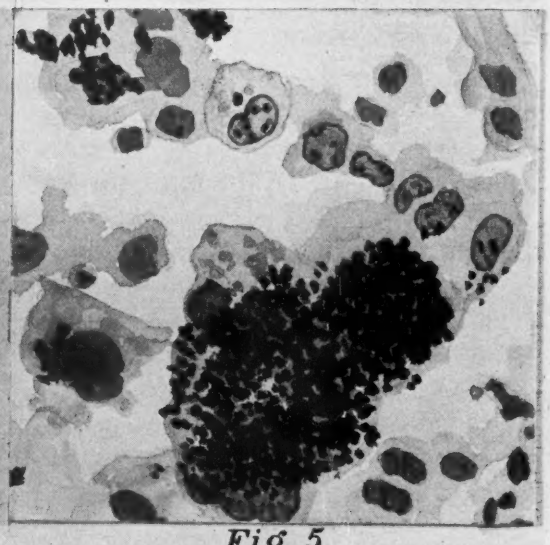

Fig. 5

FIG. 1. RIGHT LUNG, SHOWING COMPLETE BLACKENING
India ink was aspirated while animal was held on right side

FIG. 2. SAME AS FIG. 1, EXCEPT THAT ANIMAL WAS HELD SQUARELY ON ITS BACK

FIG. 3. THE CARBON WAS INSUFFLATED
Distribution also in anterior portions

FIG. 4. MICROPHOTOGRAPH OF SECTION OF LUNGS SHOWN IN FIG. 3

FIG. 5. CAMERA LUCIDA DRAWING, SHOWING GIANT CELL ALMOST FILLED WITH CARBON

A STUDY OF THE ANTIGENIC PROPERTIES OF THE LIPOIDS OF THE TUBERCLE BACILLUS[1]

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The antigenic properties of lipoids have been more closely studied for the tubercle bacillus than for any other microörganisms, but with great diversity of opinion. From the experimental facts which we have at our disposal it seems that we have no convincing proof, either that the lipoids of the tubercle bacillus play some rôle in natural or artificial immunity, or that they can produce the reaction of hypersensitiveness, local or general, in the tuberculous animal. On the other hand, there is no doubt that the lipoids give a specific serum reaction with the sera of tuberculous patients, mainly after treatment with bacillary products, and with the sera of animals treated with tubercle bacilli. We have some data to indicate that specific antibodies can be produced in animals by treating them with lipoidal extracts of tubercle bacilli (1) (2) (3). Similar is the behavior of the lipoids of *taenia* extract (4), with which it was possible to produce highly potent complement-fixing sera. Our knowledge concerning the lipoidal antigens has been greatly augmented by researches on the so called heterogenetic antigen, from the results of which it seems that there is no essential difference, according to our present knowledge, between the usual sheep haemolysins and the haemolysins associated with the heterogenetic antigen. It has been impossible to produce antibodies wth the lipoidal extracts of organs which are effective in the complement fixation and precipitin reactions. However, it has been proved that these lipoids play an important part in the production of antibodies, because the organs devoid of lipoids lose their antibody-producing properties (5) (6), and the addition of specific lipoids to a hog serum, which is not effective alone for antibody production, renders the serum effective for it (7).

The point at issue in the following researches was brought about by two observations. The first was the fact, known for several years, that the

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relative amount of the complement-fixing antibodies of patients' sera, and of the sera of animals treated with tubercle bacilli against the lipoids of the tubercle bacillus and the whole bacillus, varies to a large extent. The second circumstance was that the sera of rabbits, treated with watery extract of tubercle bacilli, have given no complement-fixation reaction with alcoholic extracts of tubercle bacilli. As a result of these observations, we aimed to determine whether we can find any exact proof that the antibodies against the lipoids of the tubercle bacillus are different from the antibodies against the other constituents of the bacilli, which corresponds to a widespread hypothesis,[2] or whether there is no specific antibody for lipoids since there may exist only one tuberculosis antibody which extends its action to the lipoid. We have attempted to decide this through the application of the Castellani experiment on the complement-fixation test.

The next step was to try to produce antibodies in rabbits with lipoids which were made with special care, and we succeeded in producing sera which are without doubt specific. For the sake of coherence we will describe first, the production of complement-fixing sera with the lipoids, and will give later our experience relative to the nature of antibodies.

The controversy over the antibody-producing ability of the lipoids and the fact that in some careful experiments the antibody-producing properties of the lipoids have been missed, necessitates a detailed description of the material and methods. We are not positive that the care we have used in handling these lipoids is essential; perhaps the same result may be obtained in a simpler manner.

In the preparation of the extracts we used five strains of tubercle bacilli, all of which are old laboratory strains and the exact history of which is unknown to us. Two of them, designated as H597 and WH, are fast-growing and can cover the surface of a litre flask of glycerine-bouillon in from thirty-six to forty-eight hours and can form a thick layer in from three to five days. The H597 can cause progressive disease when injected into a guinea pig. We have had no experience with the pathogenicity of culture WH. The other cultures, namely H-D, H-A and B-A, develop in from four to six weeks and all have a medium virulence. For preparing the extracts we used six-day cultures of H597 and WH, and four-week old cultures of the others, grown on 5 per cent glycerine-bouillon. They are washed free from bouillon with distilled

[2] Maintained in the German literature by Much and his pupils.

water in a Buchner funnel and the water is thoroughly drained off. The bacillary mass is then spread out in a thin layer, and put in a dessicator and dried *in vacuo* over sulphuric acid for from two to three days. It is then transferred to a moving grinder with 15 to 20 times as much water-free ether (Baker's ether distilled over sodium) and allowed to extract while grinding for eighteen hours. The ether emulsion is then

TABLE 1

TREATMENT OF RABBITS	TITRE OF SERUM AGAINST HOMOLOGOUS STRAIN OF TUBERCLE BACILLI			TITRE OF SERUM AGAINST ALCOHOLIC EXTRACT OF HOMOLOGOUS STRAIN OF TUBERCLE BACILLI	
Serum 7. Injected intravenously weekly from September 2, to October 14, 1922, receiving altogether 6.7 mgm. alcohol extract of strain 597	November 25, 1922	1:80	++++	1:40	++++
		1:160	++−−	1:80	+−−−
Serum 8. From September 26 to October 26, 1922, 4 mgm. alcohol extract 597	October 1, 1922	1:20	++++	1:40	++++
		1:40	++−−	1:80	+−−−
Serum 40. From November 15 to January 20, 1923, alcohol extract 597, 15.4 mgm.	January 29, 1923	1:80	++++	1:20	++++
				1:40	+−−−
Serum 11. From October 4 to December 4, 1922, alcohol extract D, 20 mgm.	December 12, 1922	1:40	++++	1:20	++++
				1:40	+−−−
Serum 37. From November 15 to December 4, 1922, alcohol extract D, 8.2 mgm.	December 12, 1922	1:40	++++	1:40	++++
				1:80	+−−−
Serum 39. From November 15 to December 4, 1922, alcohol extract, WH.	December 12, 1922	1:40	++++	1:80	++++

filtered off in a Buchner funnel *in vacuo*, and the residue is again extracted with ether for ten hours and the second ether extract is filtered off. The residue is then extracted in the grinder with water-free alcohol, in same amount as the ether, for eighteen hours and filtered in the same manner. The alcohol extract thus obtained is stored in small bottles, which are filled to the top and kept in a dark place at ordinary room temperature. The immunizing of animals was begun immediately after obtaining the alcohol extract.

In regard to the chemical composition of the alcohol extract we can only say that the dry residue contains from 2 to 3 per cent of nitrogen and an average of 2 per cent of phosphorus, and gives no biuret or Millon's reaction. We have not filtered it through a bacterium-free filter, in order not to lose any of its effectiveness. It is not impossible that the clear fluid may contain a few bacilli, but the number of them is bound to be exceedingly small. Likewise, we cannot say that no protein can be present in combination with the lipoids, but the amount of it in an extract obtained from dry material with water-free alcohol must be exceedingly small, as is proved by the analytical data.

The results of immunizing eight rabbits are shown in table 1.

The method of complement fixation used will be given in connection with the examination of the properties of the antibodies. In the tables we give the data at the time when antibodies are first clearly demonstrated. The amount of lipoids and the time necessary to produce the antibodies vary greatly in different animals. We were not successful in reaching a higher titre, mainly because we lost our animals during further treatment. The titre we reached with the sera of animals treated with the lipoid antigen was much lower against the lipoid antigen than that of the sera of animals treated with the whole bacilli, and in the latter case the rabbits received much smaller amounts of lipoids. For instance, rabbit 10 which had a titre of 1 to 600 against the lipoid antigens received altogether 13 cgm. of wet bacillary material with a fat content of nearly 4 mgm., of which only a small fraction belongs to the alcohol-soluble phosphatid.

We made the same observation in the treatment of rabbits with watery extract of tubercle bacilli. We had to use much larger quantities and treat the animals much longer in order to produce complement-fixing sera than in those treated with whole bacilli. However, there is no doubt that the complement fixation was specific. The rabbits gave no reaction before treatment with the tubercle bacillus antigens, and we rarely found that untreated rabbits gave even a weak reaction with a serum dilution of 1 to 10. The general experience that it is impossible to produce antibodies with similar lipoids obtained from the animal body removes any foundation for the supposition that the antibodies are nonspecific. In the quantity of extracts used for the immunizing experiments, which is never higher than a few milligrams, the water-soluble proteins cannot be present in an amount sufficient to account for the antibody production. A relatively large amount of the soluble proteins is

necessary for the production of antibodies and those produced have no effect with the lipoids. Therefore, even though we are not perfectly able to characterize the extracts chemically and cannot judge with absolute surety whether or not these small amounts of proteins are present, it is perfectly certain that the effectiveness of the lipoid extract is not caused by the known water-soluble proteins of the tubercle bacillus. That the antigen contained in the lipoid extract is different from the antigen contained in the tubercle bacillus emulsion or in the watery extract is clearly shown by the character of the antibodies produced. The serum obtained with the tubercle bacillus, as we shall see later in the course of the paper, ordinarily reacts in much higher dilution with the tubercle bacillus emulsion than with the alcohol extract. The serum obtained with the alcohol extract reacts nearly equally with both antigens.

In the absorption experiment with the lipoid antigens the antibodies are taken from the serum produced with the lipoids completely, while only a small quantity is taken from the other sera. Therefore, if we can presume that the water-free alcohol will dissolve a protein-lipoid compound, we shall find that the antigenic properties of this compound are entirely different from the other bacillary constituents and produce an antibody directed against the lipoid.

With the same lipoid extract as was used in the immunization experiment, we tried in many instances intracutaneous tests on tuberculous guinea pigs. We never succeeded in obtaining a positive reaction. This also excludes the possibility that the alcohol extract can have an appreciable protein content.

The absorption experiment of Castellani was used by K. Meyer (8) for the differentiation of lipoid antibodies from other antibodies, but was not a complete success because he did not succeed in removing the lipoid antigens from the mixture and probably the extracted tubercle bacillus emulsion was not perfectly lipoid-free. We have found that the mixture of the lipoid emulsion and serum, filtered through a filter paper-pulp filter, gives a filtrate which ordinarily does not check in itself and does not influence the antibodies. Our filter is a glass tube 10 to 15 mm. thick, which ends in a capillary tube 2 to 3 mm. thick and which is filled with a layer of filter paper-pulp 1 cm. thick on top of some glass wool, and the whole is packed tightly with a glass rod. The fluid goes through very slowly *in vacuo* but quite easily when centrifugated. An emulsion of lipoid in normal saline solution, such as is used in the complement fixation test, shows no checking at all when filtered in this manner.

For the estimation of the absorption properties of the protein of the tubercle bacillus, we have used a precipitate from the watery extract of fat-free tubercle bacilli obtained in the presence of 1 per cent acetic acid and 1 per cent sodium chloride, heated to 60°C. This precipitate is insoluble in water and has good antigenic properties in the complement-fixation test. A sheep-haemolytic serum treated in exactly the same manner as was used in the absorption experiment, and filtered, changed its titre only from 1200 to 600. This shows that the precipitate has very little nonspecific binding properties.

Notwithstanding that the absorptive properties of the precipitate are probably not exactly similar to the unaltered proteins of the tubercle bacillus we thought better to use it than to use tubercle bacilli which had been extracted until they were no longer acid-fast. The precipitate contains no lipoids, and with the bacilli we are never sure that all the lipoids have been eliminated and that during the extraction the proteins are not subjected to changes. Our results, that the precipitate takes out the lipoid antibodies from a serum obtained with the whole bacilli, seem to be more convincing than the same result with extracted bacilli.

The experiment is conducted as follows: 3 cc. of a dilution of serum, 1 to 10, was mixed either with the same amount of lipoid emulsion in normal saline solution (made in the usual way for the complement-fixation test) or with the described protein precipitate. The amount of lipoid emulsion must be enough to take out every antibody with which it can react and it seems to be better to mix the serum with different strengths of the lipoid emulsion. It also seems that the best filtrate is obtained when the serum and lipoids are in a determined proportion to each other. The mixture is placed in the incubator and kept over night at 37°C., and the following morning is filtered according to the method described above and titrated with the different antigens.

The mixture of serum and the lipoid emulsion ordinarily shows a flocculation after standing. We have not tried to see whether this flocculation could be used as a specific reaction as in the precipitating reaction of syphilis or as the reaction of the heterogenetic antigen.

As to the technique of the complement-fixation reaction, we used two units of complement and two units of haemolytic amboceptor with the sheep cell system. For the antigen units we used approximately the half and quarter of the checking amounts and always used two different amounts of antigen. We incubated first an hour at 37°C. on the water-bath and again half an hour after the addition of the haemolytic system.

TABLE 2

SERUM	METHOD OF TREATING RABBIT	TITRE AGAINST HOMOLOGOUS STRAIN OF TUBERCLE BACILLI		TITRE AGAINST HOMOLOGOUS STRAIN OF ALCOHOLIC EXTRACT OF TUBERCLE BACILLI	
9	Rabbit injected with emulsion of tubercle bacilli D in 0.5 per cent phenol	1:640 1:1280	++++ ++−−	1:160	++++
D	Same as above	1:80 1:160	++++ +−−−	1:20 1:40	++++ ++−−
10	Injected with emulsion 597 in 0.5 per cent phenol	1:1200 1:2560	++++ +−−−	1:640	++++
597	Same as above	1:80 1:160	++++ +−−−	1:80	++++
8	Injected with alcohol extract 597	1:20 1:40	++++ ++−−	1:40 1:80	++++ +−−−
37	Injected with alcohol extract D	1:40	++++	1:40 1:80	++++ +−−−
35	Injected with watery extract of tubercle bacilli	1:40	++++	1:10	−−−−
44	Same as above	1:80	++++	1:10	−−−−

TABLE 3

METHOD OF TREATMENT OF SERUM 9	SERUM CONTROL WITHOUT ANTIGEN		TITRE WITH HOMOLOGOUS STRAIN OF TUBERCLE BACILLI		TITRE WITH HOMOLOGOUS ALCOHOL EXTRACT	
Untreated	1:10	++++	1:320 1:640	++++ +−−−	1:80	++++
Serum diluted 1 to 10, mixed with equal amount of emulsion of alcohol extract D, 1 to 5, incubated 24 hours and filtered	1:5	+−−−	1:160 1:320	++++ +−−−	1:10	−−−−
Serum diluted 1 to 10, mixed as above with alcohol extract, with the addition of the same amount of alcohol extract, 4 hours later. Incubated and filtered			1:160 1:320	++++ +−−−		

The same lipoid was used as for injecting the rabbits. In tables 2, 3, 4 and 5 we give the results of Castellani experiments with eight sera. Four of these were obtained by injecting an emulsion of tubercle bacilli in 0.5 per cent phenolized normal saline solution, 2 with the watery extract of defatted tubercle bacilli and 2 with the alcoholic extract of dried and ether-extracted tubercle bacilli.

Table 2 gives a description of the sera used.

Table 3 is a detailed description of one experiment, and illustrates that we do not remove more of the antibodies from the serum by using repeatedly large amounts of lipoids.

TABLE 4

METHOD OF TREATMENT OF SERUM 8	SERUM CONTROL WITHOUT ANTIGEN	TITRE WITH HOMOLOGOUS STRAIN OF TUBERCLE BACILLI	TITRE WITH HOMOLOGOUS ALCOHOL EXTRACT
Untreated	1:5 ----	1:20 ++++ 1:40 ++--	1:40 ++++ 1:80 +---
Serum diluted 1 to 10 and mixed with equal amount of dilution 1 to 5 of alcohol extract 597, incubated 24 hours and filtered	1:5 ++++ 1:10 +++- 1:20 ----	1:10 ++++ 1:20 ++--	1:10 ++++ 1:20 ++--
The same, only mixed with dilution 1 to 10 of alcohol extract	1:5 ----	1:10 ± trace	1:10 ±
Mixed with dilution 1 to 20 of alcohol extract	1:5 +---	1:10 ++++ 1:20 ++--	1:10 ++++ 1:20 ++--

Table 4 illustrates the effect of the amount of lipoids in the filtrate of serum-lipoid mixture. In using the dilution of 1 to 5 of the alcohol extract the filtrate gives high checking without the antigens; with 1 to 10 there was no checking in the serum control and none with the antigens; with 1 to 20 the amount of lipoids was inadequate to remove all the antibodies which are present.

Table 5 gives a summary of the absorption experiments with the different sera and antigens. We have made quite a few additional experiments similar to those given in table 3, all of which illustrate the same properties of the lipoid serum. However, slight defects in the experiment and the loss of our animals, as previously mentioned, prevented us from giving more examples. According to our tables, the treatment with the bacillary emulsion (we always used in the absorption experiment the bacillary emulsion used in the production of the serum) takes out every kind of antibody from the sera.

TABLE 5

SERUM	METHOD OF ABSORPTION	COMPLEMENT FIXATION AFTER ABSORPTION	
		Titre with homologous tubercle bacilli	Titre with homologous alcohol extract
D	Serum diluted 1 to 10, mixed with equal amount of alcohol extract D, diluted 1 to 10; incubated 24 hours and filtered	1:80 ++++ 1:160 ±−−−	1:10 −−−−
	The same but mixed with suspension of tubercle bacilli D, previously extracted with distilled water	1:10 −−−−	1:10 −−−−
	Untreated	1:80 ++++ 1:160 ±−−−	1:20 ++++ 1:40 ++−−
597	Serum diluted 1 to 10, mixed with alcohol extract 1 to 10 (597), etc.	1:80 ++++ 1:160 ++−−	1:10 −−−−
	Serum diluted 1 to 10, mixed with suspension of tubercle bacilli 597, etc.	1:10 −−−−	1:10 −−−−
	Untreated	1:80 ++++ 1:160 +−−−	1:80 ++++
9	Serum diluted 1 to 10, mixed with alcohol extract D 1 to 10, etc.	See table 3	
	Dilution 1 to 10, mixed with 1 to 10 dilution acetic acid precipitate, etc.	1:80 ++−−	1:20 ++++ (Serum control 1-10, ++++)
	Untreated	1:640 ++++	1:160 ++++
10	Diluted 1 to 10, mixed with alcohol extract 597, 1 to 10	1:1280 ++++	1:10 ++++ (Serum control 1:5, +−−−)
	Diluted 1 to 10, mixed with acetic acid precipitate, etc.	1:40 ++++	1:20 ++++ (Serum control 1-20, ++++)
	Untreated	1:1280 ++++	1:640 ++++
8	See table 4		
37	Diluted 1 to 10, mixed with acetic acid precipitate, etc.	1:20 ++++ 1:40 +−−−	Not determined
	Untreated	1:20 ++++ 1:40 +−−−	

TABLE 5—*Continued*

SERUM	METHOD OF ABSORPTION	COMPLEMENT FIXATION AFTER ABSORPTION	
		Titre with homologous tubercle bacilli	Titre with homologous alcohol extract
35	Dilution 1 to 10, mixed with alcohol extract 597, etc.	1:20 ++++ 1:40 ++−−	
	Dilution 1 to 10, mixed with acetic acid precipitate, etc.	1:10 −−−−	
	Untreated	1:40 ++++ 1:80 +−−−	1:10 −−−−
44	Dilution 1 to 10, mixed with alcohol extract 597, 1 to 10, etc.	1:40 ++++	
	Dilution 1 to 10, mixed with acetic acid precipitate, etc.	1:20 ++++ 1:40 ++−− (Serum control 1:10, ++++; 1:20, ++−−,	
	Untreated	1:40 ++++ 1:80 ++−−	

Treatment with the lipoid emulsion destroys the reaction with the lipoid antigens. It lowers a little the titre of the sera gained with the whole emulsion, using the whole emulsion as an antigen. The serum obtained with the lipoid gives no reaction with the whole emulsion after the absorption with the lipoids. The serum obtained with the protein extract of the tubercle bacilli is not influenced at all. The sera obtained with the whole emulsion treated with acetic acid precipitation of watery extract loses every antibody, including the lipoid antibody. On account of the low titre of the lipoid sera, we are unable to state with surety whether the protein precipitate takes out the antibodies from them. From the given experiment it does not seem to be the case.

The antibodies produced in treating the rabbits with tubercle bacilli or their constituents are according to the described experiments of three kinds:

(1) Antibodies with whole affinity for the protein substance of tubercle bacilli and limited affinity for the lipoids. They are produced by the inoculation of whole bacilli. The antibodies against the lipoids and the proteins in this sera seem not to be different because both are bound by the proteins.

(2) Antibodies with only lipoid affinity are produced by inoculating the lipoids.

(3) Antibodies with purely protein affinity which are produced with the watery extract of bacilli. We cannot affirm whether we succeeded in producing sera with much higher titre with the lipoids or with the proteins. The antibodies would not digress from one antigen to the other; but the difference between the three kinds of antibodies seems, from our experiments, to be very clear. The lipoid antibodies in the sera obtained with the whole emulsion are similar to the so called group agglutinins of the bacillary agglutinins. In the case of the tubercle bacillus, it seems that one part of the group agglutinins can be produced separately with an isolated constituent of the bacillary bodies.

The facts described in this paper do not permit a definite conclusion regarding the rôle of the lipoids in immunity to tuberculosis, but they indicate the possibility of this rôle, which is supposed by many authors to be the case.

SUMMARY

With the alcohol extract of dried and previously ether-extracted tubercle bacilli, it was possible to obtain complement-fixing sera in the majority of the treated rabbits.

We give a method of applying the absorption reaction of Castellani to the complement-fixation test.

With the application of this method to rabbit immune sera, obtained with different antigens derived from tubercle bacilli, we have found that the lipoid antigen removes entirely the fixing property of the sera obtained with the lipoids. It removes from the sera, obtained with whole bacilli, the antibodies directed against the lipoids, but the titre of the serum remains nearly unchanged. They have no effect on the sera obtained with the protein extract of tubercle bacilli, which sera show no complement fixation with the lipoid antigen. The precipitate obtained from the watery extract takes out both the protein and lipoid antibodies from the sera obtained with the whole bacilli and takes out the antibodies from the serum obtained with the proteins.

In the serum obtained with the whole bacilli the antibodies against the lipoids behave as do the so called group agglutinins of the agglutination sera, but in the lipoid sera of tubercle bacilli the same antibodies can be obtained independently.

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THE DEMONSTRATION OF INCREASED NUMBERS OF TUBERCLE BACILLI IN THE EXCRETIONS OF TUBERCULOUS PATIENTS

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While studying the morphology and staining qualities of tubercle bacilli, I noticed in young (four to ten days) and old cultures (over five to eight weeks), on agar-potato media (1), in addition to Ziehl-positive bacilli, a large number of forms, which were only to a small degree acid- and alcohol-resistant, or which were even entirely Ziehl-negative. These occurred in many, even the majority of, cultures. In order then to stain all bacilli, the Ziehl-positive as well as the less acid-resistant and Ziehl-negative ones present in the same culture, I used the well known methods of Hatano, Much, Aronson, Weiss, both newer methods of Kirchenstein (2) and that of Konrich (3). I also stained the films after decolorization with Giemsa stain, according to Lubarsky's formula (4). Modifying, in various ways, the periods of staining and decolorizing, it is possible to obtain a large number of stained bacilli and to demonstrate granulations in the latter; but it is impossible, in this way, to obtain a deep and homogeneous staining of all the bacilli.

In order to stain a maximum number of bacteria, my experiments showed that not only must the films be stained twice, but between the first and second stainings the bacterial cortices must also be treated by boiling the films for two minutes in a weak solution of potash; or, better still, in a 1 per cent solution of crystallized sodium carbonate. The procedure is as follows:

1. Preparation of films: Liquid sputum can be laid on the slide in several consecutive layers, each layer being allowed to dry before applying the next one. As the background remains practically unstained by this method, it is advisable to make several layers of sputum, as this procedure will not mask the bacilli. Such is not the case when the sputum is compact, and can only be spread out unevenly, leaving masses which cannot be properly decolorized (the background appearing in such places dirty).

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2. The film is covered with carbol-fuchsin without previous fixation and held over a flame for two minutes, during which steam must appear several times.

3. Without washing the film, a 1 per cent solution of crystallized sodium carbonate is applied, which is boiled over a flame two minutes, during which it may be necessary to add fresh carbonate solution. The film must not be washed in water, but the excess of sodium carbonate is simply shaken off.

(Instead of the 1 per cent boiling solution of sodium carbonate, used between the first and second stains, one may use any sodium carbonate solution between 0.5 and 10 per cent, as well as solutions of potash, ammonium carbonate, bile, etc.; but none is better than the 1 per cent solution of sodium carbonate crystals. Thus a 1 per cent solution of NaOH demonstrates a large number of intensely stained bacilli, but only in such places where the sputum adheres well (a part of the film falls off). It is a mistake to mix the sodium carbonate solution either with the first stain (the carbol-fuchsin) or the second stain (the compound stain); and it is entirely inadvisable to treat the film with any alkaline solution before the first staining, as well as the sputum before laying it out on the glass, as all neutralizing solutions will afterward be of no avail.)

4. The stain is applied, composed of one part of carbol-fuchsin and three parts of carbol-methyl-violet (10 parts of a saturated alcoholic solution of methyl-violet and 90 parts of 2 per cent carbolic acid solution in water); and the film is held over a flame two minutes, during which steam must appear several times, without ebullition however.

5. Shaking off the excess stain, without washing in water, we treat it for five minutes with a 10 per cent solution of sodium bisulphate, adding a few drops of 60 per cent alcohol during the last stages of the decolorizing procedure.

(There is no advantage in using peroxide of hydrogen, Javelle water, permanganate of potash, acidulated alcohol, organic or mineral acids, or various solutions, instead of the 10 per cent solution of sodium bisulphate, introduced by Konrich, for decolorizing purposes. All the above and similar solutions have been used in different methods, but, according to my experience, while their use means the nondecolorizing of a part of bacilli, the majority of the bacilli lose the primary stain and take the counterstain. Moreover, the Na_2SO_3 solution is especially good when followed by a short decolorizing action of 60 per cent alcohol, as the sulpho-acid-resistance (but not the sulphoresistance alone) is equivalent to the acid-alcohol-resistance of the tubercle bacilli, a fact which I proved experimentally with bacilli of both human and bovine types. Fresh solutions of sodium bisulphate must be made every four to six days, as they easily lose their reducing power and change to sodium sulphate.)

6. Lastly, without washing the film in water, we counterstain the film by treating it with a 1 per cent solution of picric acid for 30 seconds.

(It is also possible to use very weak watery solutions of green or yellow stains for counterstaining purposes; but they cannot be compared, as regards clear-

ness of background, with the 1 per cent water solution of picric acid, which was introduced by Spengler and Tribondeau. Methylene blue and Loeffler's alkaline blue are to be particularly avoided, as is also mixing the picric acid with the alcohol and sodium bisulphate; all procedures are to be avoided in which the decolorizing is done simultaneously with counterstaining, as in the methods of Johnes, Torchetti, Rondelli and Buscalioni, Gabbet, Weichselbaum, etc.)

7. I remove all stain spots from the edges and back of the slide with a cottonwool swab saturated in alcohol and acetic acid.

8. Then only the slide is dipped once or twice in water (not washed under a free flow of water) and dried in the air (not with the aid of blotting paper). It is not always harmful to dip the slides in water or let water run on them, as there are sputa from which even a strong flow of water is unable to wash off the bacilli. As, however, water is entirely useless and does not improve the condition of the smears, while in many cases it diminishes considerably the number of bacilli, it is far better to avoid water altogether.

I stain in shallow metal boxes. The slides must be very clean and passed over a flame. If, after the use of picric acid, the slide shows insufficient decolorizing, repeat the decolorizing and counterstaining.

In order to understand the action of the respective procedures on the tubercle bacilli, I made the following experiments: Smears of human and bovine tubercle bacilli, taken from (a) young, (b) older, growing very abundantly, and (c) old, yellow cultures, were stained by different methods, and examined at various stages of staining by treating them with nigrosin (this is positive combined with negative staining, or simultaneous staining) (5). I have found that ordinary, positive staining (staphylococci with fuchsin, for example) stains only the cortical part of the bacteria, leaving the interior parts unstained. If we stain a film of staphylococci with a weak solution of fuchsin (positive staining) and examine microscopically, all the cocci are red. If we remove the cedar oil with xylol and treat the same film with a 5 per cent watery solution of nigrosin (slanting the slide so as to permit a free flow of the solution), we will, upon examination, find all cocci unstained against a dark grayish background. When, however, we remove the cedar oil again and wash off the nigrosin with water, we find the red-stained cocci. The explanation of this paradoxical phenomenon is that, during the negative staining, nigrosin adheres to the bacteria and prevents our seeing the red-stained cortical parts, so that the bacteria appear entirely unstained. However, if for the positive staining we use carbol-fuchsin instead of watery fuchsin, or if we heat during the staining, then after the negative

staining with nigrosin the central parts of the bacteria appear stained, showing that the stain acted not only on the cortex but on the interior, nuclear part also. For greater convenience let us call the stain in the first instance, *cortical* and in the second, *nuclear*.

Films of human and bovine tubercle bacilli were treated with nigrosin, after having been stained with carbol-fuchsin alone, or with carbol-fuchsin, boiling sodium carbonate and carbol-methyl-violet. The results are given in table 1.

Strong acid, when used for decolorizing, reduces considerably the number of bacteria that show nuclear staining; while sodium bisulphate does not affect the number. Some of the cortically stained bacteria even stain with methylene blue.

TABLE 1

		2 MINUTES OF HOT ZIEHL-NEELSEN	2 MINUTES OF ZIEHL-NEELSEN 2 MINUTES OF SODIUM CARBONATE 2 MINUTES OF CARBOL-METHYL-VIOLET	GRAM'S
Human tubercle bacilli	I and III stages	Mostly cortical	Exclusively nuclear	Exclusively cortical
	II stage	Mostly nuclear	Exclusively nuclear	Exclusively cortical; granules red and not violet
Bovine tubercle bacilli	I and III stages	Cortical	Exclusively nuclear	Exclusively cortical
	II stage	Nuclear	Exclusively nuclear	
Acid-resistant bacilli (Marpmann)		Nuclear	Exclusively nuclear	Mostly nuclear; granules red, not violet

The simultaneous staining proves that even a very strong stain affects the cortical and nuclear parts of the bacteria, while it leaves unstained the oval-shaped part between the cortex and the nuclei; therefore, when nigrosin is used, stained nuclei appear in stainless bacilli. When nigrosin is removed, the stained cortex gives an appearance as though the entire bacillus took the stain. The above method permits, I believe, not only the study of the structure of the bacterial cell, but may be used for diagnostic purposes as well. This method differs entirely from the Gins method (6). Gins stained his films first with Chinese ink and then with carbol-fuchsin, in order to show the filaments; while Weltmann did the same to show the cortices.

When we examine sputum, sediment from exudates and cerebrospinal fluid, urine and discharges or pus from cold abscesses for tubercle bacilli, we notice at once that, while the unstained films show a great number of bacteria, the same films, when stained by the Ziehl-Neelsen method, show a quite insignificant number. The fact that this latter method and many others demonstrate only relatively few bacilli is due to the following reasons:

1. When staining sputum films, the layer of sputum must be very thin, as the blue-colored sputum masks a number of bacilli.

2. The different degrees of acid-resistance of tubercle bacilli in various stages of development and the fact that the nuclear part of the bacilli cannot be stained without previously attacking the cortex of the bacilli have not been taken into consideration.

3. Many bacilli are not visible when carbol-fuchsin is used without an additional stain to show the nuclear part of the bacilli.

4. When we wash the stained films in water, the latter washes off, not only the stain, but also a number of bacilli.

5. When too strong acid is used for decolorizing, some of the less acid-resistant bacilli lose the stain and take on the counterstain.

6. In films which were treated too intensely with the counterstain, some of the bacilli, of which only the cortical part was stained, take the counterstain, while some bacilli are lost in the deep blue background.

It was relatively simple to overcome the difficulties mentioned under *5* and *6* by using sodium bisulphate instead of acid as the decolorizing solution and picric acid to take the place of the various counterstains. All my efforts were, therefore, directed toward removing the drawbacks mentioned under *2*, *3*, and *4*, and I believe this has been largely accomplished by the method I have described.

Sputum films need practically no fixation, ought not to be washed in water between consecutive applications of stains, and must be treated with a hot solution of sodium carbonate after the first stain.

A large number of experiments showed that the boiling of sodium carbonate on slides, previous to the application of stains, causes the disappearance of a large part of the film during the following procedures, a circumstance which no neutralization with acetic acid can prevent. The above points, and especially as regards the boiling of the sodium carbonate solution on a film between the staining procedures, are the essential part of the method described above.

Numerous experiments with this method prove that none of the suggested homogenization methods can be compared, even in slight degree,

with the sodium carbonate method, which regularly *increases the number of bacilli* on the films from *25 to 60 times*, when compared with the number of bacilli found by the Ziehl-Neelsen method, as shown in table 2.

I shall not endeavor to review the entire literature on the sedimentation or homogenization of sputum, or the various staining methods, but will discuss only some general conclusions of several authors. Thus, Philibert (7) considers homogenization indispensable, as direct examination is insufficient: "the number of bacilli is so small that simple direct examination cannot disclose them." In other words, the bacilli may be so rare, that their discovery is accidental, and direct examination, without homogenization, is fruitless. (He suggests the following interesting theory,

TABLE 2

Comparative demonstration of tubercle bacilli in the 10 sputa last examined

SPUTUM	ZIEHL-NEELSEN METHOD	NEW NUCLEAR METHOD
1	1 in every 20 to 30 fields	5 to 8 in each field
2	1 in every 2 fields	15 to 40 in each field
3	0	0
4	0	0
5	15.9 in every 2 fields	16 in each field
6	14.7 in every 2 fields	14.5 in each field
7	Uncountable numbers	Uncountable numbers
8	0	0
9	0	9.5
10	1.5	25 singly (besides groups)

which however does not appear to correspond with the results of microscopic examinations: In an ordinary examination (smear) the volume of sputum on the slide does not exceed 1 cmm.; some tuberculous sputa may contain 10 bacilli to 1 cc. or in a volume a thousand times larger homogenization would permit the discovery of approximately *all* bacilli in 2 cc.) I believe that this opinion does not correspond with facts, and this principally because the nondiscovery of bacilli in 1 cmm. of sputum may be due, not only to the small number of bacilli, but also to their low acid-resistance, which prevents demonstration by ordinary staining methods. The same would hold true even if we deal with 1 or 2 cc. of sputum, as long as we do not use special methods, such as the above described pronuclear or nuclear staining. My opinion appears to be proved by the fact that nobody has so far found one or two thousand times more bacilli with a homogenization method than are to be found by direct examination; the increase does not exceed a modest percentage.

I have no intention whatever to deny the importance of some homogenization methods; some of them may be useful to a limited extent, but

I believe that the favorable influence of homogenization is due to an influence upon the cortices of the bacilli, making them less resistant to staining. However, such methods include, at the same time, many unnecessary procedures, and do not affect markedly the number of stained bacilli. This favorable factor in various homogenization methods consists of the heating of the sputum in an autoclave to 120° (the Despeignes method (8)), homogenization with bile (9), autodigestion and autolysis (10), the action of potash solutions (11), the action of potash with antiformin (12), the action of alkalies with pancreatin (the Spengler method), the fat-dissolving action of ligroin (Lange-Nitsche), and modifications of the above methods.

If all the above and similar methods of homogenization do not give an increase in the number of bacilli, such as might be expected from the considerations mentioned by Philibert, this is due to two reasons: (1) The action of heat, potash, bile, autolysis, etc., affects to an equal degree the cortical part of the bacilli and the further staining shows only bacilli of a certain acid-alcohol-resistance, while a number of bacilli remain unstained. (2) After homogenization the adhesion of the film to the glass is diminished, even though we subsequently treat it with acetic acid, methylated spirit, sublimate, salt, ether, etc. Thus I noticed that a film, treated with a solution of potash or crystallized sodium carbonate before staining, is regularly washed off during the staining in spite of neutralization; on the other hand, exposing the film to the boiling solution of sodium carbonate during the staining or between the consecutive applications of stains, has no harmful effect whatever.

While staining, it is of great importance to take into special consideration the different degrees of acid-resistance of the bacilli, this being due, as Vandremer (13) proved, to the media on which the bacilli grow.

It is well known that among lepra and tubercle bacilli, ordinarily strongly acid-resistant, individuals are to be found which are much less acid-resistant (Zeit), and that in these, even without any decolorizing procedures, methylene blue may replace the fuchsin stain. Ehrlich declared long ago that acid-resistant bacilli, when old, are less resistant to decolorizing with acid than are younger specimens.

If we accept the morphology of tubercle bacilli, introduced by Bergel (14), we must admit that the cortical staining affects the wax-like external part of the bacilli and the nuclear staining affects the two layers of the nuclei, while the unstained space shown in negative staining represents the lipoid and albuminous parts.

With the nuclear method of staining of tubercle bacilli, and by combining it with negative staining, we are able to study the conditions of

development of the so called Firschen phenomenon (the appearance of granules in the bacilli), as well as to differentiate the homogens from the moniliforms (Piery-Mandoul classification.)

CONCLUSIONS

1. In smears containing tubercle bacilli, stained according to the cortical method (Ziehl-Neelsen), only a small number of bacilli actually present on the films will be shown, as the great majority of the bacilli do not take this stain.

2. In order to show all the bacilli, the nuclear staining method (boiling sodium carbonate and compound stain) must be used, the decolorizing must be by means of sodium bisulphate and 60 per cent alcohol, and picric acid should be used as a counterstain.

3. Though by homogenization methods we can demonstrate more bacilli than by ordinary Ziehl-Neelsen staining, this being due to the partial destruction of the cortices by alkali, this effect is largely vitiated by the fact that such films are easily washed off the slide.

4. The examination of sputum requires, in order to cover all possibilities and fulfill all requirements:

a. Staining by Ziehl-Neelsen or any "cortical" method.

b. Staining by the "nuclear" method and counting the average number of bacilli on the films stained according to both methods.

c. Staining according to ordinary contrast methods (Pick, Jacobsohn, and Gram) to show other bacteria, such as Micrococcus catarrhalis, Bacillus influenzae, streptococci, etc., which are poorly stained by the method under *a* and decolorized by the method under *b*.

d. The examination of fresh unstained films (erythrocytes, spirals, crystals, etc.)

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INFECTION AND IMMUNITY IN TUBERCULOSIS[1]

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Some diseases, such as smallpox and scarlet fever, appear to be followed by a complete immunity, and second attacks are almost unknown. Influenza and pneumonia, on the other hand, are acute diseases followed by no lasting immunity. Tuberculosis may be acute and rapid in its course, as in infancy and in primitive races, or it may be chronic, as in the adults of civilized races.

While a high degree of immunity to tuberculosis can be demonstrated in infected animals, yet no complete immunity is known. In non-susceptible animals, such as the gerbil, the tubercle bacilli introduced remain at the site of inoculation and are not carried to the regional lymph nodes. The bacilli become imprisoned in giant cells, do not multiply, are not digested, may live several years, but in time die out.

Probably on account of the coating of wax, the tubercle bacillus is very resistant to lysis. Few pathologists have seen these bacilli in process of being "dissolved" as, for instance, they have seen the typhoid and other bacilli. Yet we know there must be some digestion of tubercle bacilli, at least in part, in order to account for the sensitization following first infection. Calmette has been unable to substantiate any claim to a "lysin" having been demonstrated, but believes lytic influences may attack the products of secretion and the protoplasmic juices of the tubercle bacillus.

All our knowledge of immunity in tuberculosis dates back to the fundamental experiments of Koch, and to what is known as the Koch phenomenon. This phenomenon must be fully understood by all students of immunity in this disease and cannot be too often repeated.

In 1891, nine years after the discovery of the tubercle bacillus, Koch wrote as follows:

[1] A lecture delivered before the Veterans' Bureau Postgraduate Tuberculosis School, Fitzsimmons General Hospital, Denver, Colorado, March 14, 1923.

If one inoculates a guinea pig with a pure culture of tubercle bacilli the wound usually closes and for the first days seems to be healed. It is only on the tenth to fifteenth day that there appears at the point of inoculation a hard nodule which soon opens and forms an ulcer which persists until the death of the animal. Now such guinea pigs infected for from four to six weeks and again inoculated behave very differently. No nodule is now formed at the point of inoculation, but the next day or the day after, the site becomes hard and has a violet red color, then blackens over a spread of one-half to one centimetre. The following days the skin undergoes necrosis. The slough is thrown off leaving a superficial ulcer which heals rapidly without the neighboring lymph nodes becoming enlarged. Thus the injected bacilli behave quite differently beneath the skin of a guinea pig already infected than they do in a healthy guinea pig. This curious effect is not only with living bacilli but with dead bacilli.

This discovery led Koch to the discovery of tuberculin. He injected a watery suspension of dead tubercle bacilli into healthy guinea pigs and produced only local abscesses. Such suspensions injected into tuberculous guinea pigs killed them in from six to twenty-four hours. Koch then found that by thinning the emulsion until it was scarcely cloudy and injecting a little of this into tuberculous guinea pigs every day, or every other day, the tuberculous process improved, the discharging sinus from the first infection became smaller and scarred, weight was gained, and in some cases the disease appeared cured. These remarkable results have not been reproduced, and it is almost certain that about this part of his experiments Koch was oversanguine.

Subsequent workers have found several variations possible in the Koch phenomenon.

1. Should the second injection be made too soon after the first, the second infection behaves like a primary infection.

2. If the second infection is delayed several months instead of several weeks after the primary infection, there is usually no ulceration, only a slight swelling at the site of the second injection which quickly disappears. Yet the tissues around the site of the second infection contain living tubercle bacilli.

3. If the second infection is brought about by the transplant of a tuberculous lymph node, the lesion becomes a chronic one, opening, discharging, and closing from time to time. Recently we have produced this same effect by *first* inoculation with incubated tuberculous nodes.

4. Should the second injection be made with massive doses of virulent bacilli the site will not heal.

5. If the second injection be made with very small numbers of bacilli there may not occur any local lesion. (This is also true of first inoculation, both with free tubercle bacilli and with tuberculous tissues.)

It must be remembered that the second injections in these experiments have nearly always been made with what in human infections would be considered massive doses.

So far no experiments have been conducted to trace the exact destiny of the bacilli of the second injection.

A. S. Griffith is now engaged in such work, and his method is quite ingenious. If the first infection has been brought about by the human type of bacillus, the second injection is made at appropriate time with the bovine type of bacillus. Dr. Griffith has published much original work on the differentiation of these types, and it will be possible by methods of isolation to find out the exact distribution, if any, of the bovine type from the second inoculation.

It is of interest to note in passing that Koch in his work not only discovered the general tuberculin reaction, but also the local and focal reactions.

We must now follow systematically and in the tissues the events which follow these infections.

Of first infection we know

1. The extreme sluggishness of the local reaction. The site is visible after a week and palpable in from ten to twenty days. With small doses no leucocytes appear, but with larger doses polymorphonuclear leucocytes are present but rapidly disappear. The microscope shows a slow proliferation of endothelial cells.

After a week lymphocytes take part in the tubercle formation and they especially congregate at the periphery, the proliferating endothelial cells of the fixed-tissue type, becoming more and more fusiform from pressure, occupying the centre. Local anaemia due to pressure of the mass on capillaries occurs and favorable conditions for bacillary proliferation are established. Caseation, the cause of which is unknown and consisting of disintegration of tissue, sets in and is followed by cold abscess formation.

2. Some tubercle bacilli from the first inoculation promptly get access to the general circulation and are sifted out into distant lymph

nodes where they may remain in a quiescent state, or cause lesions with little tendency to progress.

3. The regional lymph nodes swell in two to three weeks and active disease, similar to that of the inoculation site, manifests itself.

4. The experimental animal appears well and no noticeable constitutional symptoms immediately follow first infection.

With second infection we encounter a condition of changed reaction known as "allergy."

Following second infection we find:

1. For six to twelve hours following the inoculation there is rapid inflammation at the site of injection, the height of which is reached in twenty-four hours and lasts another twenty-four hours. If the dose is large the reaction is of a haemorrhagic nature and necrosis takes place. If the dose is moderate the nodule formation disappears, but about the fourth day a firm nodule with absence of inflammation may be felt.

2. The phenomenon is due to extreme rapidity of tissue change. There is accelerated appearance of proliferation of the fixed-tissue cells and abortive progression of proliferation.

3. The regional lymph nodes may soon swell slightly but such swelling does not last.

4. As far as it is known the tubercle bacilli are held at the focus of entry, but the work of Griffith may show new light on their distribution.

5. There is a rapid intoxication of the animal and the constitutional symptoms may be severe.

6. The reaction to the bacillary protein is the result of allergy.

Many investigators in tuberculosis believe that tubercle bacilli invariably produce lesion at the site of entry, or at least in the immediate regional nodes (Cohnheim's law).

Theobald Smith states that there are many factors, mechanical, pathological, and immunological, which determine this, and that in cattle the primary lesion is often not found. He claims too that tubercle bacilli may multiply in the tissues and yet only microscopic lesion be found.

Inoculating only very small numbers of bacilli (ten or less) we have frequently failed in experimental animals to discover the site of the first inoculation.

Smith observed also in cattle infected with filaria that lymphoid cells were poured out around human tubercle bacilli which had been

injected, whereas no such lymphoid exudate was present in cattle not infected with filaria.

So too in cattle which had received two immunizing doses of human tubercle bacilli. These when inoculated with bovine bacilli reacted with a predominance of lymphocytes at the site of the new lesions and few fixed-tissue cells (the endothelial cells above referred to, often termed "epithelioid") or giant cells took part in the tubercle formation.

Smith draws attention to the interesting similarity of the reaction in parasitized cattle to human tubercle bacilli and in the partially immunized cattle to bovine tubercle bacilli. The tissues in the parasitized cattle appear to be made more sensitive by previous injury; in the latter animals the tissues seem to be more resistant through previous vaccination.

The protein of the tubercle bacillus (except possibly in large doses, Calmette) is not of itself toxic, and can produce but a faint and transient condition of allergy.

In spite of Koch's hopeful communication, quoted above, no effective immunity has ever been produced by injection of an experimental animal with dead tubercle bacilli, though Baldwin and Petroff have produced skin allergy in this way. Some time since we attempted to ascertain if dead tubercle bacilli could produce a local immunity at the site of injection. To test this question, a dense emulsion was made of dead bacilli from a culture, and several guinea pigs were inoculated intracutaneously with this. Local abscesses resulted. After several weeks the pus from these local abscesses was aspirated, and into the residual space about one hundred living bacilli of the original culture were injected. Infection of the regional lymph nodes took place as soon as if there had been no wall of tuberculous tissue to hinder, lesions of these nodes developing at the same time as in the controls.

Tuberculin reaction, the sign of allergy, only occurs in tuberculous animals and only occurs if focal reaction takes place first.

According to Krause, a guinea pig with slight and well-invested lymph node tubercle will not be made as rapidly and profoundly ill by injection of a large dose of tuberculin as it will be by reinoculation of living tubercle bacilli which would represent far less protein.

He explains the tuberculin reaction as due to:

1. A rapid degradation of bacilli into poisonous materials.

2. Absorption of focal materials from the constituent cellular elements of tubercle.

The present belief is that no true toxins have ever been isolated from tubercle bacilli. The constitutional symptoms of tuberculosis are ascribable to anaphylactic protein sensitization phenomena and degradation products of protein materials absorbed from both bacilli and lesions. The rôle of "specific" and "nonspecific" substances in the production of intoxications is at present very uncertain.

Krause has shown recently that all tissue emulsions injected into experimental animals can produce violent constitutional symptoms.

Hort some years ago found that water could prove a protoplasmic poison. Injecting water subcutaneously at daily intervals, a continued fever was produced in rabbits, with loss of weight.

The formation of tubercle is a tissue reaction for the most part and it is also an immunity phenomenon.

The regional lymph nodes, which become so soon diseased following inoculation, would appear to be the first organs to seriously oppose the bacilli. They possibly contain some factor absent in the tissues at the site of entry.

The regional lymph nodes near the site of the second inoculation may undergo a temporary slight swelling, but they do not break down. It would therefore seem that these too, like all the tissues of the body, are in a high condition of allergy and so highly immune to reinfection. It is almost certain that they are already infected, for we have found a widespread distribution of tubercle bacilli and lesions in most of the lymph nodes of the guinea pig a few weeks after first infection. The bacilli in these distant nodes appear to be held in check as they often are in the area of second infection; it may even be possible that in these nodes the bacilli may perish in time.

Agglutinins and precipitins have been shown to be somewhat inconstant in spontaneous tuberculosis, but appear in experimental disease. Opsonins may be present and fluctuate. Complement-fixing bodies appear after injection of living or of dead bacilli. In general, students of immunology have not discovered any decided influence of these sera contents on immunity processes in tuberculosis.

A kindred phenomenon associated with tubercle infection is that of anaphylactic hypersensitiveness. This condition is not accompanied by any appreciable immunity, but it can be transmitted to offspring through the female parent. The latter is true also of bodies fixing complement.

In order to clarify the comparison between allergy and anaphylactic hypersensitiveness, both of which are released by the toxic injection of tuberculin and of certain chemical fractions of tuberculin, the following table has been prepared.

Conditions of hypersensitiveness to tuberculoprotein

Allergy, or changed tissue reaction	Anaphylactic hypersensitiveness
1. Induced by infection with tubercle bacilli. No dissociated substance of bacilli has ever produced allergy in complete typical form.	1. Easily and always obtained by parenteral injection of dissociated tuberculoprotein.
2. Not transmitted through female to offspring.	2. Uniformly transmitted through female to offspring.
3. First manifestation in animal and probably in man occurs from 6 to 25 days after first infection.	3. May or may not exist after the development of tubercle.
4. Undoubted and demonstrable partial immunity always accompanies allergy.	4. No undoubted immunity to tubercle infection follows.
5. Allergy reaction may be delayed and late.	5. Anaphylactic reaction prompt.

In addition, the following qualities of allergy may be mentioned:

6. Allergy due to injection of dead bacilli usually appears to be inconstant, feeble and transient.

7. Allergy due to tubercle infection is durable and definite, lasting as long as lesion exists, except perhaps when the animal is moribund.

8. Man and sheep are highly allergic after infection, reacting to small doses of tuberculin.

9. The guinea pig is less allergic; the Pirquet test is not producible, but there is vigorous response to tuberculin injected intracutaneously; the doses however must be larger than in man.

10. The rabbit is less sensitive than other experimental animals. Intracutaneous reactions are inconstant and feeble.

11. In general, the degree and intensity of allergy parallel the degree and intensity of infection.

12. As tubercle tends to heal, allergy diminishes.

13. In human beings allergy will fluctuate as extension or sclerosis wins.

14. There is no proof that allergy lasts after infection has disappeared.

15. Allergy diminishes in intercurrent disease, as measles and influenza; also in pregnancy; possibly after fatigue. It diminishes also in phases of acute tuberculosis.

Should the work of Zinsser be corroborated some of these statements concerning allergy may be modified.

Zinsser sought to answer the following questions: In the course of a tuberculous infection does true anaphylaxis to tubercle bacillus products develop? If so is it parallel in time and intensity with intradermal (allergic) reaction?

Zinsser found:

1. Positive skin reactions were usually obtained nine to ten days after infection.

2. By employing the isolated uterus method of Dale, the animals were never anaphylactic at this time.

3. After infection had lasted three weeks both reactions could be obtained.

The next question Zinsser asked was, are these results due to two fractions? Anaphylactogens are proteins, tuberculin is probably of simpler structure.

Experiments were then undertaken to separate chemically tuberculin from anaphylactogen. By appropriate treatment of tubercle bacilli a proteose residue was obtained which was completely negative to protein tests. This residue invariably produced skin reactions as powerfully as whole tuberculin. A nucleoprotein fraction also retained tuberculin activity, and it was thought that this might be the mother substance from which the proteose fraction was derived. By treating guinea pigs with large amounts of nucleoprotein, there was a suggestion that in fourteen days positive skin tuberculin reactions could be obtained. This result would be the first approximately typical tuberculin skin reaction ever produced by an isolated chemical substance.

To the isolated uterus anaphylactic test the proteose fraction was found entirely negative.

The questions regarding the development of pulmonary tuberculosis or phthisis and the many recent discussions on reinfections are all referred to the Koch phenomenon.

It will be of interest therefore, in view of the facts briefly touched on, to discuss later the views on reinfection held by some of our leading contributors to tuberculosis literature.

Pulmonary tuberculosis is the result of reinfection in a being who has recovered wholly or in part from a primary infection.

We are not able to imitate the disease absolutely in animal experiment.

As to the manner of reinfection, whether exogenous or endogenous, there is not unanimous opinion.

The newborn calf in a domestic herd will be exposed to infection by the bovine type of tubercle bacillus.

So we must concede that a newborn child, if nursed by its mother and not fed cow's milk, will be exposed to infection by the human type of tubercle bacillus. Weaning is possibly general after eight months and then, if cows' milk is not carefully prepared, we may expect bovine infection. It is at this time that we find from the mortality statistics that the bovine death rate is highest; namely, at the end of the first year.

It is quite doubtful whether man is more susceptible to the human than to the bovine type of tubercle bacillus; indeed, it is considered by A. S. Griffith that the two types are equally virulent for man.

Experiments on animals have shown that many more bacilli are necessary to infect by the alimentary tract than by the respiratory route. It is conceded by investigators that bovine infection almost invariably takes place through the throat or through the alimentary canal, whereas human infection is almost always conveyed by inhalation.

As Griffith points out, severe and fatal infections from bovine tubercle bacilli are not so frequent because of access through the alimentary tract, and the results are less certain and severe than when respiratory infection occurs.

About fifty per cent of cervical node infection is agreed to be of bovine origin and, as Cobbett argues, this fact alone strongly opposes the view that tubercle tracks down from cervical nodes to cause pulmonary tuberculosis, which is almost invariably due to the human type of tubercle bacillus.

Newborn babies are not usually exposed to "carriers" of tuberculosis, unless born of tuberculous parents or handled by tuberculous nurses or grandmothers.

From three years upward, children's circles of acquaintances enlarge rapidly, and since one person in every fifty may be a "carrier," they must soon come in contact with the bacillus. About half of our children become infected with tubercle at from three to six years of age and, with the freedom they have at this time of coming in contact with more and more people, their infection is easily explained. The active life of such children would not keep them probably in long contact, and possibly contact is not too frequently repeated.

Such contact with a "carrier" would result in infection of a mild degree, as a rule; and this is actually what is observed. In addition, such chance infections might be advantageously spaced for the best development of allergy and so of comparative immunity.

In consumptive families, and it is from these that we get so large a number of our tuberculous patients, the opportunity for frequent and massive infection is patent.

With such children, too, the infection may be too frequently occurring for a proper condition of allergy to develop.

In many of the children of tuberculous parents we can note evidence suggesting chronic disease. The tuberculous diathesis, according to Calmette, *is tuberculosis.*

It would seem possible that repeated new infections in a child with allergy poorly developed would result in "tuberculin" reactions, possibly of mild degree, which might assist in spreading infection, or possibly at times in retarding infection.

The local sweatings, the "bilious" attacks, the slight fever, the nervous irritability and many other symptoms we are slowly recognizing as the result of sensitization. Chest development may be impaired.

In such children the X-ray gives evidence of bilateral hilum deposits, sometimes with thickened bronchial trunks. Perifocal haziness may be seen which, according to Amberson's studies, indicates allergy reaction and progressive disease. We have seen many instances in which calcification has later taken place in these hilum and peribronchial deposits.

In Bushnell's excellent work, *The Epidemiology of Tuberculosis* and in later unpublished writings entitled *A Summary of the Laws of Tuberculosis,* we glean the arguments on which he bases statements that a tuberculous subject cannot be reinfected from without, even with large doses of tubercle bacilli.

For simplification these are tabulated:

1. An infected animal goes on to die of the primary tuberculosis, yet can resist large numbers of bacilli given at a second injection.

2. Bacteremia occurs in primarily infected human beings and animals without harm, and some must enter the circulation in second subcutaneous injections. Intravenous injections in tuberculous animals are also well handled.

3. The human infant infected with a large dose of bacilli dies of generalized tuberculosis just like the animal of experiment.

4. Adults are frequently exposed to infection without becoming ill.

5. Savage tribes (adults and children) exposed to tubercle bacilli succumb to an acute type of the disease.

6. In civilized races, therefore, there is a relation between the almost universal reactivity to tuberculin and the relative immunity of the adult to tuberculous infection.

7. Only the immunized can have a local and chronic form of tuberculosis like phthisis, and only these can tolerate a tuberculous bacteremia without getting generalized disease.

8. The individual who has enough immunity to keep his chronic pulmonary process localized cannot be infected from without by bacilli alone.

9. The fact that bovine pulmonary tuberculosis is practically unknown among adults, and other forms of bovine tuberculosis are rare, although many of them consume large quantities of infected milk, shows clearly that the immunized organism is proof against even massive and frequent reinfection from ingestion.

10. In the progressive primary infection from which the animal dies the tubercle bacilli are surrounded by the poisons which they, alive or dead, give off, as well as injurious substances which may be derived from dead tissues, caseations, etc.

11. Caseation is due to the toxic products of the bacillus rather than to bacilli alone. In tuberculous pneumonia bacilli are few but caseation is extensive.

12. Bacteriolysis is not a prominent feature of tuberculosis immunity; bacilli at a distance from the original focus are permitted to live, but at the same time are rendered harmless.

13. The living cell bordering on a tuberculous lesion must maintain itself in the presence of varying poisons.

14. Defense against a poison is made more difficult by presence of other poisons, hence these border cells succumb.

15. Cavitation at focus results from injection of tuberculin and of living tubercle bacilli which are easily tolerated elsewhere in the body; in other words they suffice to destroy the vitality of the already poisoned cells.

16. The tuberculosis of the immune advances, therefore, by continuity and is lymphogenous, for only in the lymphatic system do poisons collect.

17. The escape of tuberculous emboli, the aspiration of caseous and purulent masses would be excepted.

18. Lesions of larynx and intestine can also be explained by lymphogenous continuity. The neighbouring nodes may have been infected very early and immunity becoming weakened, a spread into these organs can be imagined.

19. The theory of extension of tuberculosis in the lungs as a lymphangitis which spreads from the hilum to the periphery in a retrograde way is corroborated by the facts of radiography and also by recent work on the mode of extension of pneumonic, pneumococcus processes within the lung, which have been shown experimentally to work out from the hilum.

20. There are two kinds of infection in tuberculosis:

a. bacillary infection.

b. bacillary infection guarded and strengthened by accumulations of toxic substances.

21. There should therefore be two kinds of immunity:

a. immunity to the bacillus.

b. immunity to the tubercle bacillus and its toxic products. That there is such an immunity there can be no doubt; otherwise, no caseated focus could fail to be fatal. But this immunity is gained with difficulty and is easily lost.

We learn the following arguments from the writings of Krause:

1. It is true that infection protects against reinfection.

2. This protection is incomplete and fleeting.

3. The completeness and persistence of protection in experimental tuberculosis vary with the size of the infecting dose, and the virulence of the microörganism concerned; or, in other words, with the intensity and extent of lesion that supervenes.

4. Cattle immunized with intensive and repeated infection have protection conferred against reinfections for only a year or two.

5. There is no evidence from experiments to warrant the belief that a primary infection makes the animal immune throughout its life.

6. Comparatively heavy infections result in relatively high protection; while very small initial infections, resulting in minute lesion, bring about a resistance that may be only slightly greater than normal.

7. Infection and lesion are not fixed and absolute; they are everything from single bacilli and a few microscopic cells that soon disappear to florid multiplication of bacilli and widely diffused tissue reactions that persist and progress, or ebb and flow.

8. Resistance to tuberculous infection contingent upon primary infection has by no means an immutable standard; it is extremely slight or highly competent, transitory or remarkably permanent, and never absolute.

9. When discrete tuberculosis appears clinically in the lungs of children it begins as a rule at the roots of the lungs or has progressed from there, while discrete active tuberculosis of the adult originates in almost every case at or near the periphery of the lung, and usually at a particular part of this, namely, the summit.

10. Is it not remarkable that even when the adult human lung has massive tuberculosis, the root nodes participate relatively little in the process?

W. S. Miller has demonstrated structures of lymphoid tissue distributed along the lung lymphatics at places where bronchi, arteries and veins divide. These are found in all mammalian lungs, less marked in some animals such as the guinea pig, prominent in rabbits and man.

In experimental studies in rabbits Krause has found that soon after intravenous inoculation of tubercle bacilli these may be present in intrapulmonary lymphoid tissue. It was also noted that in guinea pigs with less development of intrapulmonary lymphoid tissue, there would be more concentration of bacilli in the root lymph nodes (tracheobronchial) than in the rabbit, the probable explanation being that the intrapulmonary lymphoid tissue of the rabbit trapped bacilli arriving from the pulmonary artery, as well as those that drained lymphatically toward the hilum.

From observations made on human lungs W. S. Miller writes, "I have followed through serial sections numerous small miliary tubercles situated in the parenchyma of the lung and in every instance I have

been able to trace their origin to one of the situations in which I have described lymphoid tissue as being present in the normal lung."

The observations of Opie, who has done such valuable work in the pathology of tuberculosis, can be summarized as follows:

1. Tuberculosis of infancy and early childhood resembles experimental tuberculosis of susceptible animals. Tuberculosis of adults does not.

a. Characteristics of tuberculosis of infancy:

Primary lesion may be anywhere in the lung, not more apt to be at apex but is usually subpleural.

There is progressive caseation with little tendency to heal. There is invariably involvement of regional lymph nodes, often more extensive than primary focus.

The primary lesion may involve the intestine and then the mesenteric nodes. This is more frequent in Great Britain than is noted in autopsies in this country.

Ready dissemination occurs, general miliary tuberculosis and tuberculous meningitis are common in infancy.

b. Tuberculosis in childhood:

There is increasing frequency with increasing age, as evidenced by autopsies and by tuberculin skin test. There is increasing tendency to healing with increasing age. Mild symptoms are associated with these healing lesions of "masked juvenile tuberculosis."

c. Tuberculosis in adults:

There is evidence (skin test, autopsy, and X-ray) that healed lesions of childhood infection are almost universal in city-dwelling adults, whether they have also evidence of subsequent active tuberculosis or not.

Apical localization of active adult tuberculosis begins to be apparent in middle childhood.

The disease is characterized by chronicity and tendency to fibrosis or to cavitation (phthisis).

There is no caseation of hilum lymph nodes draining the lesions, in contrast to the marked caseation of these in infantile tuberculosis. These nodes may be enlarged showing cellular proliferation.

The occurrence of encapsulated apical tuberculosis shown in one-sixth of the adults who die from other causes indicates that a large proportion of those who are infected never exhibit symptoms of phthisis.

It is noteworthy that apical tuberculosis is most common at that period of life at which the lesions of childhood have undergone healing and calcification.

2. The adult type of human tuberculosis may be reproduced by reinfection in animals previously inoculated with attenuated tubercle bacilli.

3. Some immunity is conferred on human beings by the focal lesions of first infection which tend to heal, but this is partial and can be overcome by massive reinfection, or by conditions such as malnutrition. It diminishes as recovery occurs and disappears when the lesions of first infection are completely healed.

4. The conception that adult tuberculosis is the result of late evolution of a childhood infection, and that adults are fully immune to new external infection, is unproved and improbable.

5. Experimental and pathological evidence goes to show that adult pulmonary tuberculosis is caused by inhalation of tubercle bacilli with the inspired air.

6. Civilized races are permeated with tuberculosis, and this permeation is their chief source of protection, but the protection is decidedly imperfect.

Baldwin and Gardner in an article entitled *Reinfection in Tuberculosis*, in which experiments on reinfection are reported and also the literature of reinfection is reviewed, write concerning exogenous reinfection as follows:

> The pathologists have demonstrated an increasing percentage of tuberculous foci in the lymph nodes and lungs from childhood to the age of universal infection in civilized peoples, which is between the fifteenth and twentieth years.
>
> From this it is evident that the first infections are not all in childhood or in immature youth. The later ones are possibly more liable to be held in the lungs, and do not affect the lymph nodes of the hilum. Our experiments lend support to this view. From year to year, successive inhalations of bacilli, if they succeed in entering the tissues, would be expected to arouse a different reaction in the tissues and one that is prone to healing or to progress in a chronic form. In other cases the subjects of the invasion fall victim to an acute tuberculosis, but in decreasing numbers as age advances.
>
> Astonishingly few cases outside of tuberculous families can be traced to definite sources of infection, and relatively few of these pursue the acute course of a primary infection as seen in the primitive peoples.

The majority of individuals who are to develop pulmonary tuberculosis for the first time after the age of twenty have already acquired it to a degree. Were it possible to discover these potentially diseased cases, who may or may not break down, we believe there would be but a small percentage not accounted for among the victims of tuberculosis in civilized countries.

Lawrason Brown in a publication, *Causative Factors in Tuberculosis*, enunciates his belief that cellular immunity outlasts by far any of the humoral indications that we have.

Arguing on the basis that inhalation infection requires fewer bacilli than ingestion and that we all breathe sooner or later tubercle bacilli into our lungs, Brown believes that some of these infections "take" and the resulting pulmonary tuberculosis is due to this second infection occurring from without in adult life. This author inclines to the belief that 50 per cent of all adult pulmonary tuberculosis is due to reinfection from without after puberty.

DISCUSSION

X-ray evidence:

1. In older people with very definite apical lesions the X-ray may fail to show definite pathological changes.

2. It is quite conceivable that some of the peribronchial tubercle deposits connecting hilum node with subpleural disease may clear away. Naegeli traced tubercle upwards to the apices of the lungs, finding at autopsy some cases where connecting tuberculous tissues in the lymph tracks could not be shown; at times only fibrous bands were present.

3. Amberson describes chronic tubercle as extending from the apex to the hilum, but notes that he has seen infection spread from one lung to another from hilum to periphery. We have made the same observation, the extension spreading out in wedge shape apparently following a bronchus and its ramifications. In the lower lobes Amberson has seen metastases distributing themselves along the course of descending trunks.

4. The first apical lesion is apt to develop on the side opposite to that in which marked hilum calcification is present; whether more apt than on the same side is not yet certain.

5. We have seen numerous instances of early phthisis in which definite extension from the hilum to the right midlobe or the lower lobes has occurred.

6. While not all apical lesions have appeared definitely connected with the hilum disease by marked and thickened bronchial lines, yet such connection would seem to be the rule.

7. Dunham and Miller have shown that the structural unit of the lung is a cone with its base to the pleura. Lymph drainage may be either toward the apex (in the direction of the hilum) or toward the base (pleura); the latter path is especially apt to function if the former is blocked. These facts are held to explain the characteristic cone shape of lesions, and particularly tuberculous lesions, of the lungs ("Dunham fans").

Pathological evidence:

Opie, in autopsies on British soldiers killed in France, found than in 27 per cent calcific mesenteric nodes were present. In such cases focal lung tubercle was almost invariably absent and calcific bronchial nodes were very rare. In St. Louis Opie noted that in only two of eighteen instances in which healed mesenteric lymph nodes were found, encapsulated apical lesions were also found. Ghon believed that he proved that tuberculous bronchial nodes were never primary but always secondary to a focus in the lungs. Opie agrees with this, finding primary lung foci in various stages of recovery from caseous nodules encapsulated with fibrous tissue, with deposits of lime salts, and with complete calcification surrounded by a fibrous mass. Opie states that after eighteen years of age such foci are invariably to be found.

Cobbett, and also Martha Wollstein and Bartlett, have found tuberculous tracheobronchial nodes with complete absence of primary lung lesion.

Cobbett, while at times finding cervical and other lymph nodes are sterile as regards tubercle bacilli, has rarely found sterile tuberculous tracheobronchial nodes. He feels that possibly bovine infection in nodes may tend to die out, whereas tracheobronchial node infection is almost invariably human in type and does not tend to die out.

Would it not rather seem probable that the infection of these nodes is constantly being reinforced? The tracheobronchial nodes collect tubercle bacilli and may be considered depots for bacilli reaching the lungs, whether through inhalation or from the general circulation. This is Krause's view.

Pathology suggests therefore that the tracheobronchial nodes are infected in all human beings after eighteen years and that this infection remains more or less quiescent. It is possible that repeated exposure may indeed keep them constantly activated.

Skin tuberculin tests:

1. There are no reports of serial tests on the same individuals over a very long period, showing fluctuations independent of coincident infectious disease, pregnancy, etc.

2. There are no reports of serial tests in which the reaction fades away and there is a negative reaction over a long period.

3. In general there is a uniform increase of positive reactions with increasing age, and in adults it is usual to find that 100 per cent will react.

CONCLUSIONS

If infection should die out, as Krause and Opie suggest, we should expect to see more frequently in adults the acute form of tuberculosis seen in primitive races and in the Senegalese troops in France, unless some immunity should possibly exist after definite healing. We have no evidence that such is ever demonstrated. Even in country dwellers, in whom the opportunity for early infection to die out might be expected, we do not find any prevalence of acute tuberculosis of the type seen in primitive man.

If infection were constantly renewed through failure of immunity from first infection or subsequent infection, we should expect to find at autopsy evidence of multiple primary infections, unless all reinfections tended to focus at strategic points such as the bronchial lymph nodes.

It is quite possible that apical lesion may develop from some bronchial lymphoid tissue which has been infected and that it is not necessary that all lung lesions should spread from the hilum nodes outwards. It seems probable that the usual course of development of a tuberculous lesion of the lung is as follows: (1) A lymph node becomes diseased and the passage of lymph through it to the hilum is obstructed. (2) The lymph current in the corresponding cone-shaped sector of the lung is reversed, and lymph flow, and with it spreading disease, extends in the direction of the pleura.

It would seem that the burden of proof for the ideas advanced above would fall on such investigators as Opie and Krause, who maintain that the protection afforded by primary infection against subsequent infection from without is imperfect and variable, rather than upon Bushnell, who feels that this acquired immunity, while not sufficient in many cases to prevent extension of disease in the injured tissues in continuity with the primary focus, is sufficient to counteract new

infection from without. If this is correct, the tuberculin-reacting urban adult incurs no risk whatever in associating with individuals who have active tuberculosis.

In arranging this lecture the writer has quoted freely from the writings of Bushnell, Calmette, Theobald Smith, Opie, Krause, and others.

The author is indebted to his colleague Dr. Chas. T. Ryder for valuable criticism and suggestions.

TUBERCULOSIS MORTALITY IN RELATION TO ALTITUDE, HUMIDITY AND DENSITY OF POPULATION[1]

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The relation between climate and tuberculosis is a question which has always intrigued physicians and no doubt savages and their medicine men have puzzled over it since the dawn of thought, or since man's first encounter with the disease. Nevertheless, it still remains in the foggy regions of speculation and prejudice. The available data are so inadequate and present such complex difficulties of interpretation that it has been the natural thing to ignore them and to form opinions untrammelled by any attempt to learn the facts.

Ichok, in a recent study (1), has tried, with full recognition of the perplexities involved, to put the problem on a rational basis. He divides France into seven climatic regions which are described with reference to temperature, humidity, rainfall, altitude and wind; and compares their tuberculosis mortality, general, urban (towns of more than 5,000 inhabitants) and rural. Allowing for possible sources of fallacy, he concludes that climatic factors have an influence on tuberculosis mortality, though this influence is only relative, not absolute; that "the climate of Auvergne takes first place (with the lowest mortality) which is to be attributed to the altitude of the region;" that "the bad effects correlated with humidity and frequent rains are apparent in the climatic regions of Brittany and Paris" (rural as well as urban).

We have undertaken to make a similar study for the United States, making use of the data provided by the United States Census Bureau, Weather Bureau, and Geographic Survey. We tabulate these data by states for which mortality figures are available, showing the approximate mean altitude, humidity (when available), density of population, and death rates from tuberculosis (table 1). The figures on humidity are approximate averages taken from several stations over a period of

[1] Read at a meeting of the American Climatological and Clinical Society, Niagara Falls, New York, May 23, 1923.

TABLE 1

STATE	APPROXIMATE MEAN ELEVATION IN FEET	APPROXIMATE MEAN RELATIVE HUMIDITY	POPULATION PER SQUARE MILE	DEATH RATES PER 100,000 INHABITANTS		
				Tuberculosis—all forms	Pulmonary tuberculosis	Nonpulmonary tuberculosis
Delaware	60	80	113.5	146.0	131.7	14.3
Florida	100	80	17.7	104.1	95.1	9.0
White				67.1	59.7	7.4
Colored				176.8	164.4	12.4
Louisiana	100	76	39.6	141.2	132.7	8.5
White				80.9	74.4	6.5
Colored				236.2	224.5	11.7
Rhode Island	200	81	566.4	131.3	110.6	20.7
New Jersey	250	82	420.0	114.0	102.0	12.0
Mississippi	300	78	38.6	127.8	121.2	6.6
White				47.8	44.7	3.1
Colored				201.2	191.5	9.7
South Carolina	350		55.2	120.0	111.9	8.1
White				65.5	58.9	6.6
Colored				172.0	162.5	9.5
Maryland	350	74	145.8	146.8	132.1	14.7
White				110.4	99.7	10.7
Colored				326.6	292.0	34.6
Massachusetts	500	77	479.2	113.8	96.9	16.9
Connecticut	500	75	286.4	119.4	103.8	15.6
Illinois	600	75	115.7	100.6	89.1	11.5
Maine	600	78	25.7	103.8	85.1	18.7
Indiana	700	72	81.3	108.8	92.9	15.9
North Carolina	700	84	52.5	116.5	106.4	10.1
White				82.8	75.3	7.5
Colored				194.2	178.2	16.0
Kentucky	750	76	60.1	152.9	133.9	19.0
Missouri	800	71	49.5	106.9	97.9	9.0
Ohio	850	73	141.4	102.8	88.3	14.5
Michigan	900	81	63.8	83.6	72.0	11.6
New York	900	74	217.9	120.9	106.1	14.8
Tennessee	900	76	56.1	164.6	145.2	19.4
White				129.3	112.8	16.5
Colored				312.6	281.1	31.5
Virginia	950	79	57.4	142.9	128.9	14.0
White				94.8	84.1	10.7
Colored				256.2	234.6	21.6
New Hampshire	1000		49.1	97.0	81.4	15.6
Vermont	1000	77	38.6	81.8	67.0	14.8
Wisconsin	1050	74	47.6	85.6	74.0	11.6
Pennsylvania	1100	75	194.5	105.0	91.5	13.5
Minnesota	1200	78	29.5	89.6	77.1	12.5
Washington	1700	78	20.3	98.4	81.5	16.9
Kansas	2000	56	21.6	48.2	41.2	7.0

TABLE 1—*Concluded*

STATE	APPROXIMATE MEAN ELEVATION IN FEET	APPROXIMATE MEAN RELATIVE HUMIDITY	POPULATION PER SQUARE MILE	DEATH RATES PER 100,000 INHABITANTS		
				Tuberculosis—all forms	Pulmonary tuberculosis	Nonpulmonary tuberculosis
U. S. A.*	2500		35.5	113.2	99.8	13.4
Nebraska	2600	65	16.9	43.0	35.4	7.6
California†	2900	77	22.0	159.6	141.8	17.8
Oregon	3300	75	8.2	89.1	73.2	15.9
Montana	3400	70	3.8	75.1	65.6	9.5
Utah	6100	43	5.5	39.1	32.0	7.1
Colorado†	6800	45	9.1	225.4	212.5	12.9

* Registration States.

† Includes great numbers of imported cases: see text.

years, and usually based on observations made at 8 A.M. and 8 P.M. The word *approximate* should be stressed, for the data provided by the Weather Bureau on this important point have not been adequate in the past; at present they are being rapidly and greatly improved. Future reports will cover drying and cooling rates, which are the resultant of relative humidity and air movement, and have been shown by Leonard Hill to bear an important relation to metabolism. The figures on population density are from the 1920 census and those on death rates from the 1920 mortality statistics. It did not seem feasible to take averages over longer periods, as a number of states have only recently entered the registration area; and while death rates fluctuate, the relation of state to state in this respect remains fairly constant.

Before attempting to correlate, even in the roughest way, the tuberculosis death rates with any of the factors considered, it is necessary to analyze this table and make some exclusions from it. As regards states with a very large negro population, the Report of the Census Bureau calls attention to the very much higher mortality from tuberculosis in this race than among whites, and cautions against making regional comparisons without allowing for this; we therefore exclude the Southern states. The same Report says, "There are many localities to which persons afflicted with this disease (tuberculosis) are attracted because of climatic conditions favorable to the treatment of this disease. States and cities which annually show high death rates from tuberculosis (all forms) are not always those which have conditions tending so the development of tuberculous diseases, but often are health re-

torts." On the strength of this obvious fact we have excluded Colorado and California, the registration states having the largest number of imported tuberculous invalids.

It will be noted that the death rate from tuberculosis (all forms) in Colorado in 1920 was 225.4. A recent study by Sewall (2) indicates that less than 17 per cent of these deaths are among native Coloradoans. The rate for Denver in 1920 was 318.1, but the deaths from tuberculosis "contracted in Colorado," as determined by the Denver Department of Health, were less than 16 per cent of the total. In 1905 one of the present writers (C. F. G.), who had been studying the matter closely since 1889, wrote, "At Colorado Springs, with a population of from 15,000 to 30,000, there has been but one (fatal) case each year originating among the native population. . . . . I have no record of other forms than pulmonary, but meningeal, glandular or bone tuberculosis is not more frequent than in other places, although a large proportion of our children have a tubercular parentage" (3). During the past eleven years the deaths from nonimported pulmonary tuberculosis have averaged 2.1 per year in a population of about 30,000, possibly half of which is made up of health seekers and their families. Even if we assume that only 10,000 are natives and therefore indisputably candidates for tuberculosis "contracted in Colorado," this still gives a rate of only about 20 per 100,000, or about one-seventh the rate for the country at large during the same period. Such data however are open to more criticism than the rest of the material with which we are dealing, and we have no similar reports from California; so we have thought best to omit these two resort states from the graphic correlations.

For the remaining group of 22 states[2] we have prepared diagrams showing the death rates per 100,000 from tuberculosis (all forms) in relation to altitude, humidity, and density of population (charts 1, 2 and 3). It is clear that many possible sources of misinterpretation still remain. A state with a very small population per square mile may have a large percentage of that population crowded into one or two cities. A state with a high mean altitude may have most of its population living along the coast, practically at sea level. A dry state may report a rather high relative humidity because the stations are located in the more humid sections, or vice versa. We do not mean to

[2] Twenty-one states in the case of humidity. No figures available for New Hampshire.

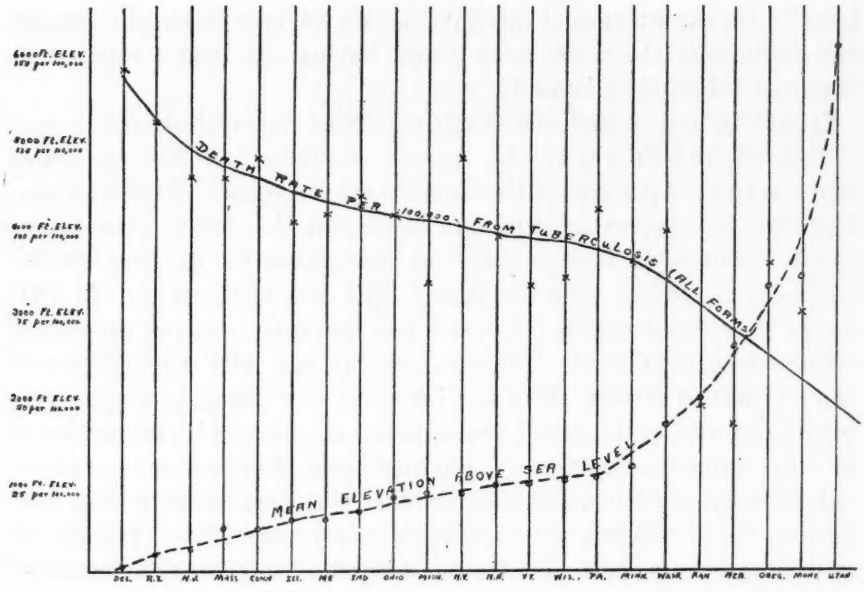

CHART 1. CURVES OF ALTITUDE AND TUBERCULOSIS MORTALITY PLOTTED TOGETHER

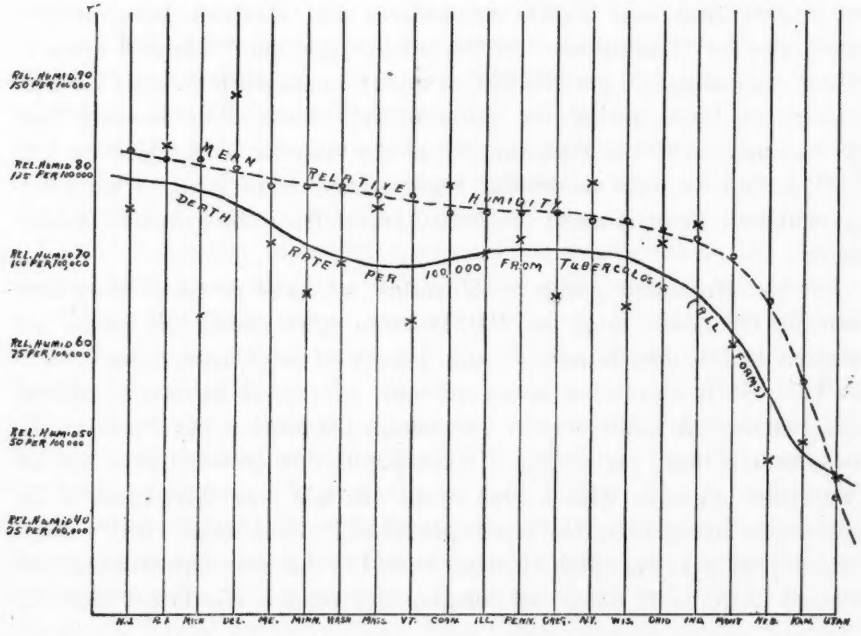

CHART 2. CURVES OF RELATIVE HUMIDITY AND TUBERCULOSIS MORTALITY PLOTTED TOGETHER

draw any dogmatic conclusions from the material presented, but merely to offer it, following Ichok's good example, as a contribution to the study of climate in its relation to disease.

With this insistent disclaimer of any conclusive certainty, we may note some inferences suggested by the curves. In general, the states showing high mortality are those which combine low altitude, high humidity, and marked density of population, such as the industrial coast states; while the states showing decidedly low death rates are

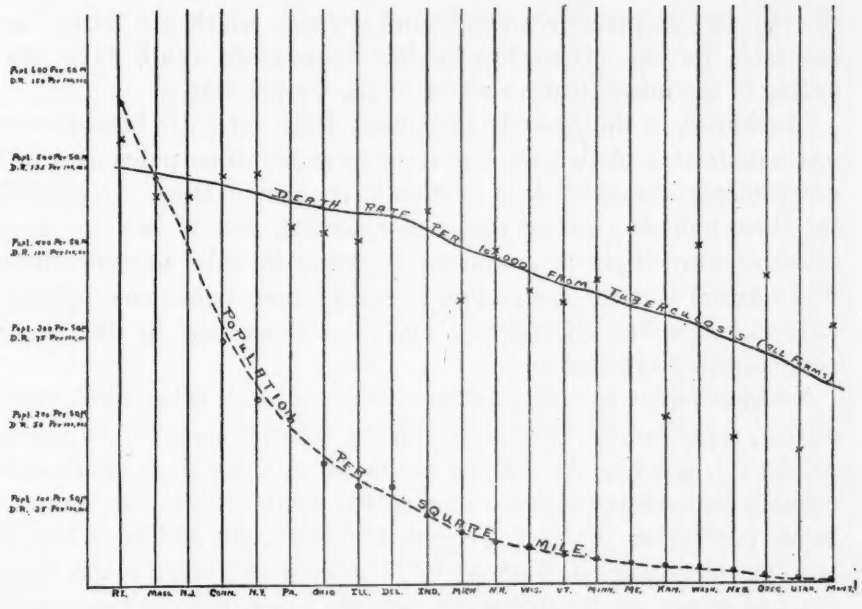
DEATH RATE PER 100,000 FROM TUBERCULOSIS (ALL FORMS)
POPULATION PER SQUARE MILE
RI. MASS. N.J. CONN. N.Y. PA. OHIO ILL. DEL. IND. MICH. N.H. WIS. VT. MINN. ME. KAN. WASH. NEB. COLO. UTAH. MONT.

CHART 3. CURVES OF POPULATION DENSITY AND TUBERCULOSIS MORTALITY PLOTTED TOGETHER

high, dry, and sparsely populated, as exemplified by the inland plateau states. The average rates for the latter region are half or less than half those of the former. Whether we arrange the states in order of ascending altitude, decreasing humidity, or decreasing population density, the same group of states occupies the first division, and the same group the last division; and the curve of mortality, drawn in relation to each of these other curves as a basis, falls in a more or less similar way on each chart. However, they are not exactly the same; and inspection, verified by a rough mathematical analysis, shows that

the correlation between death rates and climatic factors is somewhat closer than that between death rates and population densities. Moreover the low death rates of the favored states (about 40 per 100,000) are not only much lower than the general rate for the registration states as a whole (113.2 per 100,000), but much lower than the rural rate for that area (108.1 per 100,000).

From these facts we think it fair to infer that while scarcity of population, character of population and industries, relative absence of poverty, and so forth, are of great importance, there are in addition climatic factors, notably altitude and dryness, which are largely accountable for the extraordinarily low tuberculosis death rates prevailing in the inland plateau region of the United States.

In addition to the general tuberculosis death rates, we have for our own satisfaction plotted the curves of mortality from pulmonary and nonpulmonary tuberculosis in relation to the same factors. In general, the three mortality curves ran closely parallel, and it does not seem desirable to multiply or complicate diagrams in order to show them. The relation between descending mortality from pulmonary tuberculosis and ascending altitude was somewhat closer than in the case of nonpulmonary tuberculosis.

A recent report by a Committee of the National Tuberculosis Association, appointed to collaborate with the Senate Committee on Indian Affairs (4), provides data which enable us to make some crude comparisons between the regional tuberculosis death rates in this race and in the population at large. Feeling that this might add something to the valuable studies of Bushnell (5), Cummins (6), Deycke and Much (7), and others, on the differences between tuberculosis in races which have long been accustomed to it and races to whom the disease is new, we analyzed these data in the same way (table 2). Relative density of Indian population could not be determined. As regards altitude and dryness, the correlation with tuberculosis death rates which appeared to exist in the case of the comparatively immune general population is entirely wanting in the case of the susceptible savage. It was impossible to draw a resultant curve of mortality rates, which were scattered helter-skelter all over the chart (chart 4). There seemed to be greater susceptibility in those Indians living in the newest parts of the country, and hence having the shortest racial history of exposure, but this was not constant enough to be stated as a fact.

It is of course true, in general, that the more immunity exists already, the more it can be exalted by favorable conditions to which an organism of low resistance will not respond. This general statement probably applies in the case of the Indians. However, it has been reported that in South America the Indians of the high Andes show much lower tuberculosis death rates than those of the plains (8). As regards another

TABLE 2

STATE	APPROXIMATE MEAN ELEVATION IN FEET	APPROXIMATE MEAN RELATIVE HUMIDITY	INDIAN POPULATION	INDIAN DEATHS FROM TUBERCULOSIS	INDIAN TUBERCULOSIS MORTALITY PER 100,000
Florida	100	80	454	0	0
Mississippi	300	78	1,400	10	714
North Carolina	700	84	2,432	6	248
Michigan	900	81	1,093	7	640
New York	900	74	6,072		
Wisconsin	1050	74	9,713	52	535
Iowa	1100	70	345	3	870
Minnesota	1200	78	12,378	69	558
Oklahoma	1300	70	15,028	66	439
Washington	1700	78	9,639	71	736
North Dakota	1900	71	9,018	65	721
Kansas	2000	50	1,466	4	272
South Dakota	2200	70	22,649	197	870
U. S. A.			336,337		446(?)
Nebraska	2600	65	2,461	11	447
California	2900	77	13,241	69	521
Oregon	3300	75	4,042	25	618
Montana	3400	70	12,374	114	921
Arizona	4100	38	42,400	153	361
Idaho	5000	63	4,048	43	1,062
Nevada	5500	50	10,900	23	211
New Mexico	5700	45	21,530	220	1,022
Utah	6100	43	1,641	5	305
Wyoming	6700	57	1,748	6	343
Colorado	6800	45	796	11	1,382

class of highly susceptible material, namely, experimental animals, we noted some years ago (9) that rabbits inoculated with bovine tubercle bacilli seemed to live longer at Colorado Springs (6,000 feet) than at sea level; and we have recently observed the same thing in the case of guinea pigs inoculated with human tubercle bacilli, though the differences are neither great nor constant. The number of lymphocytes and mononuclear leucocytes in the blood is increased in these animals,

as in man, at high altitudes, and we believe this fact to have a bearing (much discussed but not yet explained) on resistance to tuberculosis.

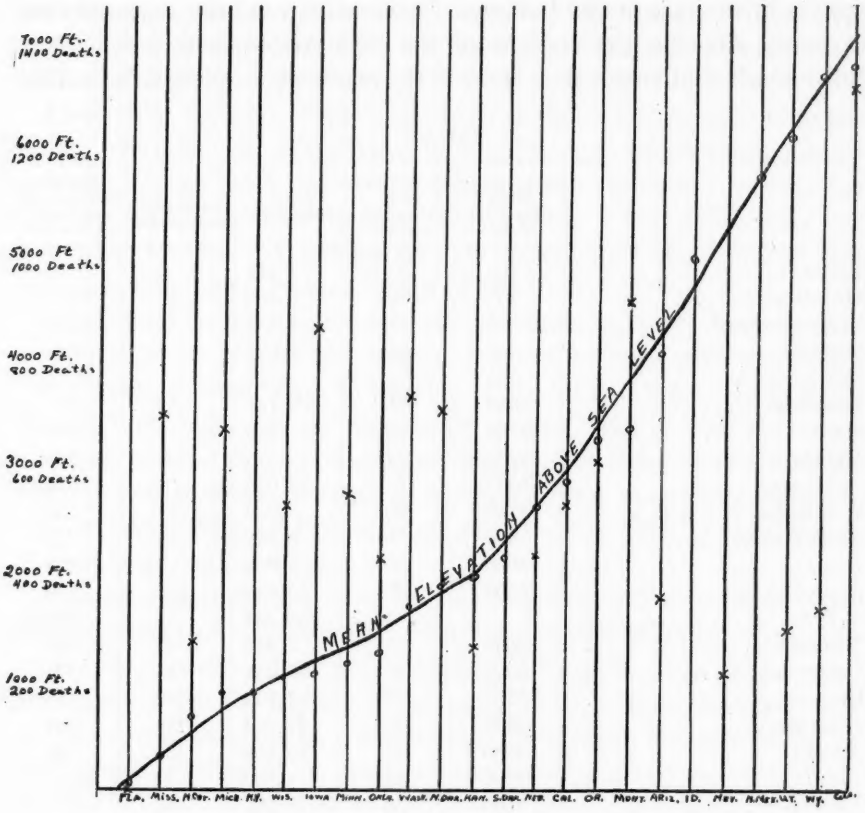
7000 Ft.. 1400 Deaths
6000 Ft. 1200 Deaths
5000 Ft 1000 Deaths
4000 Ft. 800 Deaths
3000 Ft. 600 Deaths
2000 Ft. 400 Deaths
1000 Ft. 200 Deaths
MEAN ELEVATION ABOVE SEA LEVEL

CHART 4. ALTITUDE AND INDIAN TUBERCULOSIS MORTALITY PLOTTED TOGETHER

CONCLUSION

The high inland plateau region of the United States has a remarkably low death rate from tuberculosis, both pulmonary and nonpulmonary, as compared with lower and damper regions; and this appears to be due not only to favorable hygenic, economic and social conditions, but also in considerable part to climatic factors, notably altitude and dryness.

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ALTERATIONS IN ENDOTHELIAL PERMEABILITY AND THEIR RELATION TO THE TUBERCULOUS FOCUS[1,2]

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In one of his recent essays Krause (1) has justly criticized both the looseness with which we commonly use the term "resistance" as well as the nebulous ideation apparent in discussions of this subject. He has grouped (a) lymphatic resistance, (b) cellular fixation and (c) specific immunity, as fixed points about which our views concerning resistance to tuberculosis might be crystallized.

As a matter of fact, the major part of experimental work in tuberculosis for the past thirty years has centered about the third concept and has, therefore, been strictly specific in orientation. It does not appear to have resulted in an advance of our knowledge of the disease or its therapy commensurate with the tremendous effort expended. During this time humoral antibody reactions have been hopelessly confused with allergic phenomena, and far-reaching deductions have been drawn from experiments on rabbits and guinea pigs that can by no means always be applicable to tuberculosis in man.

Particularly, the study of the focal reaction has become hopelessly confounded in a maze of immunological hypotheses. This has done much to retard the proper estimation of both its therapeutic possibilities and its therapeutic dangers, as the case might be. In view of the intimate biological connection between resistance that depends on cellular fixation (the walling off of the tubercle) and the various phases of the focal reaction, we believe that a study directed more particularly in this direction, rather than along immunological lines in the narrower sense, might have a direct value in the effort to make more concise at least one of these factors in "general resistance."

[1] From the Department of Pathology and the Laboratory of Physiological Chemistry, College of Medicine, University of Illinois, and the Laboratory of the Municipal Tuberculosis Sanitarium, Chicago.

[2] Presented at the Nineteenth Annual Meeting of the National Tuberculosis Association, Santa Barbara, California, June 20–23, 1923.

Before entering into a discussion concerning factors that may influence the focal reaction, it may be proper to state briefly our present conception of the processes that are concerned in the mechanism of the reaction, and their relation to healing and repair.

If we go back in the history of the therapy of tuberculosis but a short time, we find that Landerer (2) was the first to clearly grasp and emphasize the fact that the focal reaction might be therapeutically useful and that the reaction might be elicited with certain drugs. He introduced cinnamic acid and its salts for this purpose.

Landerer's work was carried on during the early tuberculin era and met with unusual scepticism, in part no doubt due to the current obsession that in tuberculin a "specific" had finally been found. Landerer found the obstacles insurmountable, since prejudice against any agent not of specific bacterial origin was too great; but his theoretical basis is nevertheless of great interest and quite in line with our present conception of the therapeutic possibilities that can be expected from alterations in this particular phase of resistance. In the second edition of his book, he formulates his views as follows:

> When faced with the problem of therapeutically influencing a chronic disease such as tuberculosis, we have two methods of approach. One may in the first instance seek some specific, such as quinine in malaria, iodides or mercury in syphilis, etc. The other and less empiric path leads from the direct observation of the normal method of healing of the tuberculous lesion endeavoring to bring about scar formation in tuberculous processes. But the majority of the tuberculous processes with which we have to deal clinically show little tendency to scar formation, primarily due, I believe, to the lack of an inflammatory reaction of sufficient degree. If we regard inflammation as a purposeful biological process, the object of which lies in the destruction of the noxious agent, then the relative lack of an inflammatory reaction in tuberculosis can partly explain the difficulty observed in the spontaneous cure of the lesion.
>
> Our problem lies in the production of an inflammatory reaction of such character that scar formation will result; to do this I have sought to bring about an aseptic inflammation by chemical means.

In view of the fact that the focal reaction is not an antibody reaction, despite current concepts to the contrary, we will in the following discussion omit reference to the lymphatic as well as the immunological phases of resistance, without of course prejudicing their importance. By this means we perhaps may avoid confusion, since the focal reaction

can be adequately explained on biochemical and physical alterations quite independent of immunological reactions in the specific sense.

In broad terms, the secondary tubercle consists of a necrobiotic area in which cellular degeneration has been brought about by extracellular enzymes liberated by the tubercle bacilli, by toxic metabolic products liberated by them or by the actual presence of bacteria in the cytoplasm of the cell. Liquefaction necrosis, the common outcome of acute inflammation, does not take place. Several factors contribute to this peculiarity of tubercle. Among these factors are the absence of polymorphonuclear leucocytes, the maintenance of a relatively unaltered hydrogen ion balance, the lipoidal nature of bacterial remains which may act as antitryptic agents, and the relative isolation of the focus from the blood stream through which end-products of digestion could be removed.

The cells that fix and localize the process are of varied origin. There are the endothelial syncytium, normally destined as itinerant first aid, and reparative cells in milder types of injury; the resident connective tissue cell stimulated to greater functional and formative effort; and, finally, the lymphocyte, perhaps "attracted" by the circumstance that waxes and fats are to be digested. In the lower animals variations occur in the type and relative importance of the various cells taking part in the reaction. Thus in the dog, which we have studied in greater detail, the endothelial elements seem to dominate to a greater extent than in man.

Endothelial cells normally function as regulators of the physiological exchange between the vascular channels and the tissue cells. We know from the work of numerous biologists (Lillie, Osterhout, Embden, Schade, Gildermeister, Ebbeke, to mention but a few) that the property of altering the surface permeability is inherent in every cell; and, in general, it may be stated that increased function (activity, work, irritation) is associated with an increased permeability. Rest is associated with diminished permeability. Increased function may go over to fatigue, in which case permeability is increased and the alteration at the surface film becomes less easily reversible. With the death of the cell it becomes freely permeable. In sensitization we deal obviously with an alteration in the speed and extent of these membrane changes, although the direction of the alteration is not changed. Normally, the endothelial cell may be altered by stimuli coming through the nervous system, directly from the blood stream or from the tissues which

the capillaries are passing. In the endothelial cell the alterations are, to some extent, of greater importance than in the ordinary parenchymal cell, because it acts as a membrane and changes in the permeability of the surface film affect not merely the passage of fluids and solids to the interior of the individual cell, but modify the passage of substances to the tissues beyond.

Assuming, then, that the vascular endothelium is a relatively labile biological structure, stimulation should result in an increased passage of plasma through the cell wall, the tissue fluid should be more concentrated in proteins and we might expect that a relative increase in the larger aggregates (fibrin and globulins) might be found in the fluid that passes the wall. But the process is freely reversible, and after the stimulus has ceased a reversal of the surface film should set in with a diminution in the passage of fluids, a lowering of the protein content and a relative increase in the smaller colloidal aggregates (albumen). If, on the other hand, the stimulus goes on to fatigue the permeability becomes greater, even formed elements may now readily pass the membrane and the reversal of the surface film may be delayed or absent. In a sensitized cell (as in tuberculosis) the whole process is shortened and the stage of fatigue may supervene much more rapidly.

Let us now turn to the *quiescent tubercle.* This represents an even balance of biological forces. Endothelial phagocytosis and intracellular digestion have diminished the number of bacteria; alterations in the carbon dioxide tension, as suggested by Corper, perhaps retard the growth of the remaining bacteria. Connective tissue proliferation and maturation have fabricated a definite, though perhaps insecure, limiting membrane about the focus to effectually prevent the egress of bacteria-containing cells or free bacteria to adjacent lymph spaces.

Two modifications of this picture must be considered when we deal with clinical tuberculosis: (1) Encapsulation may have proceeded to a firm sclerosis that is resistant to the common alterations in the activity of the adjacent tissue (healed lesion); or (2) the limitation may be incomplete or entirely wanting, the tubercle consisting of a relatively loose aggregate of newly formed cells, a bacteria-rich and toxic mass of necrotic debris at the centre, and the whole structure relatively permeable and particularly susceptible to alterations in permeability because of at least four factors that influence the permeability of the cells—factors such as the fact that the cells are young, that many are of endothelial origin, that they are under a constant stimulus (irritation)

and therefore on the verge of fatigue, and, finally, that they are specifically sensitized. Such a tubercle will permit the rapid diffusion of toxic material (and bacteria) from the focus, as well as of mobilized antibodies, enzymes and tissue metabolites into it. Such a focus must, in its very nature, be readily influenced by every physiological or pathological alteration in the activity of adjacent tissue.

These three forms represent in broad outline both the clinical as well as the pathological forms of the disease with which we have to deal: (1) The balanced lesion, occasionally advancing, occasionally stationary, usually fibrocaseous, the most common of our clinical forms; (2) the indurative, sclerotic or fibroplastic type, of indefinite duration and (3) the exudative or rapidly advancing type. In the indurative type the degree of intoxication (irritation-stimulation) originating from the bacteria or the cell debris is negligible, the cells at the focus are relatively impermeable, and the opportunity for formative and reconstructive activity of the cell is enhanced. When the degree of intoxication is great (from bacteria or debris) relative impermeability gives way to permeability (fatigue and death of the cells) and we have the typical picture of the exudative tuberculous process. Aschoff (3) in his recent discussion takes practically this position when he emphasizes that it is not the seat of the primary infection and reinfection, nor the extent of the tuberculous process developing therefrom, that decides the clinical curability of pulmonary tuberculosis, but the character of the process, whether productive or exudative.

EXPERIMENTAL

Our experiments have been made in connection with a detailed study of the changes in the thoracic lymph following tuberculin injections, during the course of which we have studied rate of flow, protein concentration, protein fractions, sugar, bile pigment, phosphates, electrical conductivity and carbon dioxide content. These have been published elsewhere (4). We have, in addition, studied the permeability of the endothelium by means of hemoglobin injections, noting the time when the hemoglobin makes its first appearance in the lymph after intravenous injection. Hemoglobin has, for several reasons, seemed to us more suitable than any other dye, primarily because it is not foreign to the body and should therefore not in itself produce capillary injury; and second, because the size of the molecular aggregate is very close to that

of serum albumen, and will therefore be a good measure of capillary permeability for colloids of this size. Hemoglobin solutions are used to test membrane ultrafilters. Our solutions of hemoglobin were prepared as follows: Dog corpuscles were washed, laked with a small amount of ether, the proteins precipitated with aluminum cream, filtered, the clear hemoglobin solution made isotonic and warmed and an air current passed through the solution until all traces of ether had disappeared. The normal time of passage of the hemoglobin from the capillaries to the thoracic lymph should be determined for each sample because variations occur. Injections are made slowly (20 cc. in five minutes). Usually the hemoglobin appears in the lymph from ten to fifteen minutes after intravenous injection. When the lymph is clear, colorimetric determinations can be made, the standard being the amount present in the blood plasma after the injection of the hemoglobin.

From previous experiments made with anaphylactic and peptone shock (5) we have determined that, with increased capillary permeability, hemoglobin appears very promptly in the thoracic lymph (within five minutes, that is, the time that crystalloids usually take to make the passage). With diminished capillary permeability, as after adrenalin (6), the appearance of the hemoglobin is retarded, making its appearance from twenty to thirty minutes after intravenous injection.

Our thoracic duct operations were all made under local anaesthesia, a point that should be emphasized, because when a general anaesthetic is used great alterations take place in the permeability of the capillaries.

We present, first, a complete protocol of a lymph experiment of this type (table 1). The animal had been inoculated with a relatively non-virulent strain of tubercle bacilli, December 24, 1922, and was injected with 0.5 cc. O.T., intravenously, on January 25, 1923. At autopsy only minor tuberculous lesions were to be observed in the lungs and liver, all more or less translucent and gelatinous in appearance, firm and evidently healed. The alterations in the lymph under these conditions are quite typical.

Comment: The injection of the relatively large dose of tuberculin was followed by a (1) moderate lymphogogue effect that persisted for approximately an hour. (2) The protein of the lymph increased almost 15 per cent after the injection, then diminished below the preinjection level at the end of the hour. These changes are usually associated with an increased permeability of the capillaries (stimulation) with the normal reversal that commonly follows a moderate stimulus. The

(3) increase in fibrin, the (4) increase in phosphates, (5) sugar and (6) relative increase in globulins seem to be related to liver stimulation and

TABLE 1

Protocol 1, of dog 473, weight 10,000 grams, inoculated December 24, 1922, and given 0.5cc. O.T. on January 25, 1923

SAMPLE	TIME	VOLUME PER 4 MINUTE PERIOD	PROTEIN IN MGM. PER cc.	FIBRIN	EUGLOBULIN	PSEUDOGLOBULIN	FIBRIN AND GLOBULINS	ALBUMEN	SUGAR	PHOSPHATE	ELECTRICAL RESISTANCE	CARBON DIOXIDE	HEMOGLOBIN per cent
1	9:45–10	3.0	41.4	3.3	0.8	15.5	19.6	80.4	157	3.45	4.92	0.60	
2	10:00–10:15	2.0	41.6	3.8	0.6	15.4	19.8	80.2	157	3.13	4.92	0.57	
	0.5 cc. O.T. intravenously												
3	10:15–10:20	3.25	41.2	4.8					172	3.23	4.48	0.56	
4	10:20–10:25	4.6	47.9	4.8					194	3.57	4.8	0.58	
5	10:25–10:30	4.3	47.5	6.5	1.4	16.5	24.4	75.6	169	3.31		0.58	
6	10:30–10:45	3.66	42.6	6.1	0.7	16.5	23.3	76.7	166	3.29	5.04	0.60	
7	10:45–11:00	3.3	41.5	6.0	0.5	16.1	22.6	77.4	170	3.33	4.79	0.60	
8	11:00–11:15	3.9	40.2	4.4	0.3	14.3	19.0	81.0	162	3.21	4.92	0.62	
9	11:15–11:30	3.3	39.9	3.75	0.3	14.3	18.35	81.65	165	3.33	4.92	0.64	
	20 cc. hemoglobin solution intravenously												
10	11:30–11:35 11:35–11:40 11:40–11:45	2.86	41.45	3.4	1.2	15.5	20.1	79.9	157	3.74	4.72	0.60	
11	11:45–11:50 11:50–11:55* 11:55–12:00	3.0	41.7	4.0	0.8	16.3	21.1	78.9	155	3.33	4.86	0.59	5
12	12:00–12:05 12:05–12:10 12:10–12:15	2.2	42.3	5.4	0.7	15.0	21.1	78.9	149	3.41	4.73	0.58	12
13	12:15–12:30	2.7	40.4	3.4	0.25	13.5	17.15	82.85	135	3.52	4.92		15

* First trace of hemoglobin here.

usually follow the endothelial alteration. The carbon dioxide curve gives no evidence of an acidosis, nor is there much change in ionization (except the temporary increase in conductivity immediately following

the injection of the tuberculin). When hemoglobin was injected at 11:30 o'clock its appearance in the lymph was somewhat retarded (the endothelium had already become less permeable).

EFFECTS OF TUBERCULIN ON HEMOGLOBIN PERMEABILITY OF NORMAL DOGS

In the second protocol (table 2) are shown the effects of a simultaneous injection of 1 cc. of 1 to 10 O.T. with 20 cc. of hemoglobin solution

TABLE 2

Protocol 2

DOG 451, JANUARY 3, 1923, WEIGHT, 9600 GMS., NORMAL ANIMAL				DOG 452, JANUARY 3, 1923, WEIGHT, 11000 GMS., HEMOGLOBIN CONTROL			
Sample	Lymph sample Time	Sugar	Hemoglobin	Sample	Time	Sugar	Hemoglobin
1	10:00–10:15	146		1	12:00–12:15	88	
2	10:15–10:20*	175		2	12:15–12:20†	87	
3	10:20–10:25	172		3	12:20–12:25	98	
4	10:25–10:30	133		4	12:25–12:30	88	
5	10:30–10:35	144		5	12:30–12:35	84	
6	10:35–10:40		Distinct color	6	12:35–12:40		Faint trace
7	10:40–10:45	140	Marked color	7	12:45–12:50		Trace
8	10:45–11:00	126	Marked color	8	12:50–12:55	84	11 per cent
9	11:00–11:15	125	Marked color	9	12:55– 1:00	100	16 per cent
Blood plasma, 10:25		110		10	1:00– 1:15		
				11	1:15– 1:30		
				12	1:30– 1:45	111	31 per cent
				Plasma, 12:25		104	

* During this period 20 cc. of hemoglobin with 1 cc. of 1 to 10 O.T. was injected intravenously.

Lymph too turbid for colorimetric reading.

† 20 cc. of hemoglobin solution during this 5 minute period.

(dog 451) together with the control animal that received hemoglobin alone (dog 452). Sugar determinations were also made on the lymph.

Comment: The tuberculin in the normal dog, in the dose given, has produced little increase in permeability, the only difference being in the fact that the concentration of hemoglobin that has appeared in the lymph is somewhat greater in the animal that received tuberculin.

While the effect in increasing the permeability is almost negligible in the normal dog here shown, we have repeatedly demonstrated that, if the tuberculin is given at some time previous to the injection of

hemoglobin, there is evident retardation of the appearance in the lymph, that is, the endothelium seems to have become less permeable.

The following protocol illustrates this effect:

Protocol 3: Dog 447, 5 cc. of 1 to 500 O. T. injected intravenously at 10:30 A.M. and 20 cc. of hemoglobin solution injected intravenously at 1:15 P.M. First trace of hemoglobin appeared in the lymph after twenty-five minutes. Turbidity too great for titration.

Dog 450, 1 cc. of 1 to 10 O. T. at 10:30 A.M. and hemoglobin at 11:30 A.M. First trace of hemoglobin in lymph at 11:55. The titration was as follows:

Sample 1	10:30–11:35[3]	20 cc. of hemoglobin injected.
2	11:35–11:40	
3	11:40–11:45	
4	11:45–11:50	
5	11:50–11:55	
6	11:55–12:00	First trace of hemoglobin in lymph here, 2.5 per cent
7	12:00–12:05	8.5 per cent
8	12:05–12:10	
9	12:10–12:15	
10	12:15–12:30	10 per cent
11	12:30–12:45	18.5 per cent

In chart 1 the effect of a previous injection of tuberculin in two other normal dogs is illustrated. The hemoglobin used in these experiments came through into the lymph stream in considerable concentration within ten minutes after the injection, while in both animals that had received tuberculin the appearance was considerably delayed.

SENSITIVE ANIMAL

When we turn now to a sensitive animal with recently healed tuberculosis, we find that when tuberculin is administered together with hemoglobin, it appears very rapidly in the lymph stream. This is shown in chart 2 of dog 465. This animal had a healing tuberculosis (natural infection); at autopsy two small gelatinous scars were found in the lung, minute perivascular lesions in the liver and an old fibrous scar in the right kidney. It will be noted that the control injection of hemoglobin appeared in the lymph of a normal dog at a slower rate.

[3] Here also the hemoglobin required twenty-five minutes before it appeared in the lymph stream.

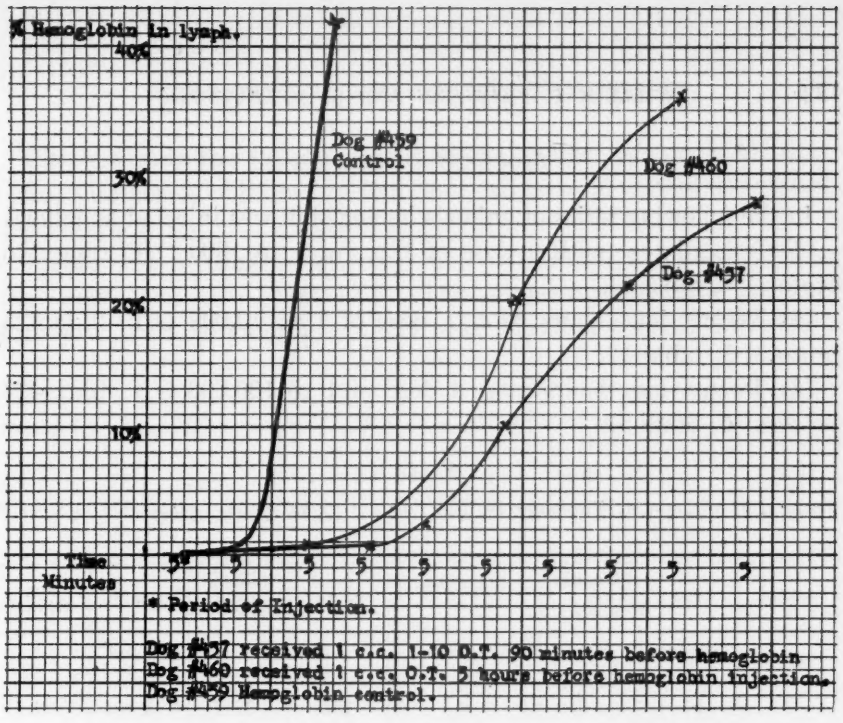

CHART 1. RETARDATION IN APPEARANCE OF HEMOGLOBIN IN LYMPH FOLLOWING INJECTION OF TUBERCULIN

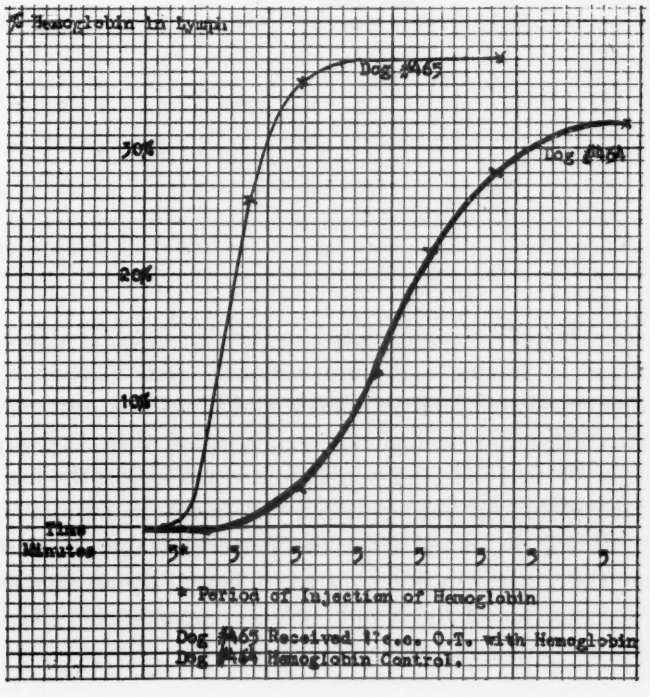

CHART 2. SHOWS APPEARANCE OF HEMOGLOBIN IN LYMPH WHEN THE FORMER AND O. T. ARE INJECTED AT THE SAME TIME

INOCULATED ANIMALS

In the following series of animals hemoglobin was injected as follows:

(1) Immediately with a dose of 1 cc. of 1 to 1000 O.T. (dog 426, protocol 4, table 3).

(2) Twenty-four hours after a dose of 1 to 10,000 O.T. (dog 425, protocol 5, table 4).

(3) Twenty-four hours after a dose of 1 to 100,000 O.T. (dog 427, protocol 6, table 5).

TABLE 3

Protocol 4, of dog 426, November 14, 1922, weight 10,000 grams, inoculated October 8, 1922

SAMPLE	TIME	VOLUME PER 5 MINUTES	HEMOGLOBIN IN LYMPH	SUGAR	PROTEIN IN MGM. PER CC.	FIBRIN	BILE PIGMENT
	minutes	*cc.*				*per cent*	
1	10	25	0				
2	10	2.7	0	122	37.7	3.6	0
3	10	2.0	0				
4	5*	1.6	0				
	5	1.6	0	110	42.8	2.3	0
5	5	2.6	Faint trace				
6	10	1.6	1/250	121	46.7	2.5	0
7	10	2.0	1/64				
8	10	2.6	1/32		47.5	4.2	0
9	10	2.1	1/32	130	47.5	3.8	0
10	10	1.25	1/32				Trace
11	10	1.25	1/32	127	45.1	3.1	
12	10	2.1	1/32				

* 20 cc. of hemoglobin solution plus 1 cc. of 1 to 1000 O.T., injected during this 5 minute period.

These animals had been inoculated on October 8, 1922, with a virulent mixed culture of bovine and human bacilli. At autopsy a marked miliary tuberculosis of the liver, spleen and lungs was observed.

Comment: When the hemoglobin was injected with the larger dose of tuberculin (1 to 1000) the permeability was evidently increased, a trace of hemoglobin appearing within ten to fifteen minutes after the injection. It will be noted from the protocol (table 3) that in this experiment the tuberculin injection was followed by an increase in the protein concentration of the lymph and the appearance of bile pigment after about an hour and twenty minutes.

The results in the two animals that received smaller doses of tuberculin, with hemoglobin twenty-four hours afterward, showed an interesting variation.

In protocol 5 (table 4) will be found the lymph analysis following the injection of 1 to 10,000 O.T. The animal was evidently not very sensitive, little lymphogogue effect was apparent and no increase in

TABLE 4

Protocol 5, of dog 425, November 13, 1922, weight 8300 grams, inoculated October 8, 1922

SAMPLE	TIME	VOLUME PER 5 MINUTES	TOTAL PROTEIN IN MGM. PER CC.	PLASMA SUGAR	FIBRIN	BILE PIGMENT
					per cent	
1	10:30–10:45	3.0	36.0	133	3.0	0
2	10:45–11:00	3.1				
Injected 1 cc. of 1 to 10,000 O.T.						
3	11:00–11:15	3.8	33.4	115	3.2	
4	11:15–11:30	3.4	33.5		3.0	
5	11:45–12:00	5.2	33.0	133	3.3	0
6	12:00–12:15	3.3				
7	12:15–12:30	2.9	32.2	133		
8	12:30–12:45	2.6				
9	12:45– 1:00	2.1	29.6	133	4.7	0
10	1:00– 1:15	3.1				
11	1:15– 1:30	3.9	34.0		5.8	
12	4:15– 4:45	2.6	33.7		3.5	
Next morning						
13	9:30– 9:45	4.5	35.2	133	4.2	0
14	9:45–10:00					
Plasma			64.4	133		0

At 10 A.M., November 14, 1922, 20 cc. of hemoglobin solution was injected. First trace of color in lymph after thirty minutes. Animal then killed. Marked miliary tuberculosis in liver, lungs and spleen.

protein took place. Indeed, the protein was considerably diminished, fibrin was increased (liver stimulation) and no bile pigment was observed. Evidently no injury occurred later from a possible stimulation of the tuberculous lesions scattered in the various organs, because the lymph the following morning contained only the normal amount of protein. Hemoglobin injected at this time did not appear in the lymph until thirty minutes after the injection.

In dog 427 (protocol 6, table 5) the injection of tuberculin was followed by the opposite effect (continued permeability and fatigue). Thus it will be noted that while the immediate effect of the injection (1 to 100,000, resulted in no lymphogogue effect, but a diminution in the amount of lymph protein, after twenty-four hours the amount of protein had actually increased over the preinjection level (about 8 per cent). Hemoglobin injected at this time came through within five minutes after the injection.

TABLE 5

Protocol 6, dog 427, November 16, 1922

SAMPLE	TIME	VOLUME IN 5 MINUTES	PROTEIN IN MGM. PER CC.	FIBRIN	SUGAR	HEMOGLOBIN
	minutes			*per cent*		
1	40	4.8	48.4	6.0	117	
			1cc. of 1 to 100,000 O.T. injected			
2	5	4.8				
3	5	4.4	46.3	5.6	146	
4	10	3.7				
5	3	4	48.1	5.3		
6	55	3.7	38.0	6.7	129	
7	30	3.6	37.4	6.4	113	
			Following morning			
	10	5.9	52.7	8.8	111	
8	5*	4.2				
9	5	4.5	51.5	9.1	93	Trace here
10	5	5.2				Marked
11	5	3.3				Marked
12	5	4.1	52.2	8.0	109	Marked
13	5	3.1				Marked

* 20 cc. of hemoglobin solution injected during this period.

DISCUSSION

From a consideration of the data here presented, we may conclude that in the normal animal the injection of tuberculin is followed by a transient stimulation of the endothelium (increased permeability), followed by a relatively prompt reversal during which time the endothelium is less permeable. Should chronic inflammatory lesions of any nature exist in the body (blastomycosis, leprosy, arthritis) the increase in permeability may be sufficiently great to initiate a focal reaction. If some condition exists such as asthma, improvement may

follow the injection of tuberculin when the state of impermeability supervenes (van Leeuwen (7)).

When we inject tuberculin in an animal with sensitized endothelium a considerable lymphogogue effect, with relatively prolonged increase in permeability, may take place. If no labile tuberculous areas are present in the body no focal reaction will result.

When we inject tuberculin in a tuberculous animal one of several possibilities must be considered. The endothelium may respond with an increase in permeability that may persist for a long time (shock effect); or the endothelium may respond with a relatively short period of increased permeability and then become less permeable. In the latter case two possibilities still may enter. The foci may be stimulated and, as a result, sufficient toxic material may diffuse out to cause a secondary effect on the capillaries. Or the foci may be only transiently stimulated and then become less permeable, in which case practically no secondary effect will be observed in the capillaries. This would be the condition usually desired in therapeutic effects.

We should like to call attention to the work of Meyer-Bisch (8). Meyer-Bisch has studied the effect of the water balance of the tissues after the injection of tuberculin, arsenic, salt and sugar. It is well known that a daily fluctuation of the water balance of the body takes place, varying from 500 to 1500 gm. per day. The weight of the individual is greatest in the evening, at which time the blood is most concentrated. It would seem that as a result of the increased metabolic activity of the day (digestion, muscular movement, etc.) the capillaries have gradually become more permeable and water has passed to the tissues. During the course of the night this again enters the vascular bed and is given off largely through the lungs. Meyer-Bisch examined a series of 32 moderately advanced cases of tuberculosis after tuberculin injection (0.5 to 1 mgm. O.T., without febrile reaction) for changes in the water balance, and observed that in 70 per cent distinct alteration from the normal could be determined.

The change in the large majority consisted in a dilution of the blood in the evening instead of a concentration, lasting in some instances several days. In general the reactions could be included in the following groups:

(1) Those in whom the blood became more concentrated, with loss of weight and general clinical regression.

(2) Those followed by a dilution of the blood and increase in weight, which would persist for a considerable period of time; this to be followed by a reversal, with the blood becoming more concentrated and the patient losing weight.

(3) Finally, those in whom the injection was followed by an immediate and continued dilution of the blood, with a continued increase in weight.

These are changes that can be readily understood on the basis of alterations in endothelial permeability which Meyer-Bisch has suggested and such as those which we have demonstrated in this and related papers. The first group consists of those cases in which the injection of tuberculin is followed by an increased permeability of the endothelium, followed by an increased permeability of the foci, this in turn followed by an increased diffusion of toxic material from the focus and further stimulation of the vascular endothelium to the fatigue stage (continued permeability). The blood becomes more concentrated, water is lost from the lungs and kidneys (diuretic effect) and the patient loses weight.

In the second group the injection is also followed by a short period of stimulation of the endothelium, with fluids passing out into the tissues, but the reverse sets in promptly and the endothelium becomes relatively impermeable. The patient gains weight (retains water in the tissues). Then however the secondary change takes place. The foci in the body have in the meantime been stimulated, have become permeable and toxic material has diffused out from them, the time varying from a few hours to several days. This will then secondarily injure the endothelium with a resulting increase in permeability (protocol 6, table 5).

The third group consists of those cases in which the dose is relatively small or the foci resistant. The dose of tuberculin produces only a transient stimulation (which may be apparent, as in protocol 1), followed by a continued impermeability (as in protocol 5, table 4). In this group no further toxic material diffuses out from the foci and the relative impermeability may be maintained.

Tuberculin differs from other agents only in the fact that the cells of the infected body react more rapidly and more violently to it, but the general direction and effect is the same as when other agents are used, such as small injections of salt, sugar, arsenic, cinnamic acid, etc., all of which bring about alterations in endothelial permeability of the nature which we have discussed for tuberculin.

We have emphasized the importance of alterations in permeability, both of the cells at the focus, as well as the vascular endothelium, because such alterations apparently have a distinct bearing on the type of lesion that results from the infection. It also seems probable that many of our therapeutic measures influence endothelial permeability, if they are at all effective, to some degree. Some of these, like salt, tuberculin, cinnamic acid, adrenalin, quinine, calcium, peptone and vaccine seem to lessen permeability when given in small doses. Some may have a primary lymphogogue effect, but are evidently followed by relative impermeability of considerable duration, the latter seemingly the alteration on which the therapeutic efficacy depends. In a second group may be placed a number of biological reactions, which, because the degree of alteration may be difficult to control, may be followed by injury, such as reactions to irradiation with X-rays, sunlight, exercise, etc.

The first group of agents is usually associated with a depression of allergic phenomena, a diminution of metabolic activity, an increase in antienzyme, and, objectively in tuberculosis, with a tendency to depress the febrile curve, to diminish night sweats, bronchial secretion and nervous irritability, and to increase weight. In the second group, in which the degree of alteration can be but with difficulty controlled, injury and activation may frequently follow.

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HEMATOLOGICAL STUDIES ON EXPERIMENTAL TUBERCULOSIS OF THE GUINEA PIG[1]

I. BLOOD MORPHOLOGY, ARNETH COUNTS AND COAGULATION TIME IN NORMAL AND UNTREATED TUBERCULOUS GUINEA PIGS

STUDIES ON THE BIOCHEMISTRY AND CHEMOTHERAPY OF TUBERCULOSIS. XXVII

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This work was undertaken to determine whether changes in the blood might serve to indicate the effect of methods used in chemotherapeutic experiments on tuberculous animals. The present report consists of the results of examinations made on the blood of normal and untreated tuberculous guinea pigs. We are now making similar examinations of treated tuberculous animals, for diagnostic and prognostic purposes, in testing the value of the drugs under experiment. A report of this work will appear later.

A review of the literature of studies on the blood in human and experimental tuberculosis shows little unanimity as to the blood changes that occur in this disease. Indeed, this was to be expected on account of the complexity of the disease itself and the differences in its manifestations in tuberculous adult patients, who have been studied in most cases, and in the nonsensitized guinea pigs that are used for experimental work.

REVIEW OF THE LITERATURE

On human tuberculosis:

The earlier hematological studies in human tuberculosis have been carefully reviewed by Ullom and Craig (1) and Klebs and Klebs (2). These reviews bring out the complete lack of uniformity in the results of routine clinical blood counts in tuberculosis. Although it is fairly generally agreed that a moderate anemia of the secondary type prevails, in which the decrease

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of hemoglobin is relatively greater than that of the red blood cells, there is no agreement as to whether the latter are increased, normal or decreased in the first and second stages. Even in the third stage, normal or increased counts are reported by some workers, though a progressive decrease of red corpuscles is reported by the majority.

Sokolowski (3) and Applebaum (4) claimed that variations in the red blood count, with frequent increases of erythrocytes above normal, are common, and are due to changes in the blood concentration from profuse sweatings, expectoration and diarrhea. But Grawitz (5) believed the variations were due to the effects of the bacilli which cause a transudation of serum from the tissues into the blood.

Irregular variations were also found in the leucocytes, but it was generally thought that an increase in the neutrophilic polymorphonuclear elements indicated the advent of a mixed infection and that such were found more commonly in the later stages.

Neither do workers agree as to the reaction of the lymphocytes to tuberculosis. Thus, Ewing (6) found an excess in all mononuclear cells in acute and most chronic cases; but Strauss and Rohnstein (7) were impressed with the fact that the mononuclear percentage tended to decrease with the progress of the disease. While the results of the counts at the Phipps Institute (1) seemed to indicate that an actual increase in lymphocytes corresponded to an increase in resistance, Ullum and Craig believed that the point was not fully established.

Reports of the reactions of eosinophiles are also inconstant. Several workers found them normal in the early stages, but absent or decreased in severe cases. Zappert (8) believed them to be decreased in febrile cases, but increased with or before a fall in temperature. Halborn (9) thought that an increase in eosinophiles indicates resistance to the disease. Swan (10) believed that an eosinophilia was prognostically favorable.

More recently there has been less analysis and publication of routine blood counts; but we find Solis-Cohen and Strickler (11) reporting an increase of lymphocytes with improvement in pulmonary tuberculosis and an increase of polymorphonuclear cells as the patient grows worse. Weil (12) found a steady decrease in lymphocytes and eosinophiles as the disease progressed. Yokoyama (13) found the red blood count and hemoglobin normal until the third stage, when they both decreased, but the hemoglobin more rapidly. Lymphocytes decreased as the disease advanced. Eosinophiles were normal until the last stage when they were slightly decreased. McDougal (14) suggested that the rapid variations in leucocytes might be due to chemotactic or anaphylactic influences and that this so called "leucocytic swing" might have diagnostic and prognostic value. Cummings (15) believed that a high percentage of lymphocytes was indicative of an increased resistance.

From these reports the tentative conclusions might be drawn that in clinical tuberculosis there frequently appears a mild chlorotoid anemia, a variable red blood count possibly due to changes in the blood concentration, a leucocytosis in cases of secondary infection, and a lymphocytosis and eosinophilia if a resistance is developed to the tuberculosis.

On experimental tuberculosis:

In recent years there has been an increasing number of studies on the changes of the blood picture in experimental tuberculosis. In 1901 Achard and Loeper (16), working on rabbits and dogs, noted a primary increase in the polymorphonuclear elements, which subsided in a few days and was followed by an increase in eosinophiles and mononuclear elements. A polymorphonuclear leucocytosis might reappear later. Claude and Aly-Zaky (17) found that the eosinophiles appeared in the beginning of the infection and remained high in circumscribed fibrous cases, but disappeared rapidly in acutely advancing cases. Gaertner and Roemer (18) showed that extracts of tubercle bacilli, injected intravenously into dogs, produced a change in the lymph flow, which they believed to be caused by an alteration in the relation between the blood vessels and the tissues in the interchange of lymph. Hussey (19) concluded that guinea pigs, rendered relatively immune to virulent tuberculosis by avirulent bacilli, show an increase in lymphocytes, as they did also in avirulent tuberculosis, and that the greatest activity of the lymphocytes occurred at the period of greatest reaction to the infection. No such lymphocytosis, but an irregular leucocytosis, occurred in virulent tuberculosis. Rogers (20) found a fall in lymphocytes which became quite marked in the later stages. A preliminary sensitization with an avirulent strain of tubercle bacilli, followed by inoculation with virulent bacilli, caused little or no change in the leucocyte picture from that observed in nonsensitized animals. Murphy and Sturm (21) found that tuberculous guinea pigs exposed to dry heat showed an increase in lymphocytes and an increased resistance to tuberculosis. But Corper and Gauss (22) in a similar experiment observed that all animals, whether exposed to dry heat or not, showed a steady decrease in lymphocytes. Taylor and Murphy (23) found that guinea pigs, in which lymph tissue and lymphocyte count had been reduced by X-rays, were more susceptible to tuberculosis. In the last stages of tuberculosis in guinea pigs McJunkin (24) found an increase in endothelial leucocytes which persisted until the animal died.

METHODS AND TECHNIQUE

Our experiments were carried out on healthy male guinea pigs, of uniform weight and inoculated subcutaneously in the inguinal region with pure cultures of human tubercle bacilli. They received no other treat-

ment and were left to the usual laboratory care until death, after which they were carefully autopsied. Normal animals, living under the same conditions but in different cages, were also studied as controls.

Routine blood counts were made at intervals of from one to three weeks, the shorter periods being used in the acute cases and the longer ones in the chronic cases or normal animals. The study covered a period of twenty-one months, from April 1, 1921, to January 1, 1923. Many of the chronic cases and normal animals were examined during this whole period. Over 700 complete blood examinations, besides several special studies discussed later, were made. Forty animals were studied throughout their disease until death. Seven normal animals were examined over the same period, and isolated counts made on a score of other normal animals.

The usual clinical methods were employed. Blood was obtained by pricking the large vessels of the ear. Red and white corpuscles were counted in Türck counting-chambers, using Hayem's solution and 0.3 per cent acetic acid with methyl violet. Hemoglobin was read by the Sahli instrument. Coverslip smears were stained with Wright's stain. All examinations were made in duplicate, and if the duplicate counts did not agree a third examination was made. Leucocytes were classified as lymphocytes, large mononuclears, transitionals, neutrophilic polymorphonuclears, eosinophiles, and basophiles. In making the charts the various leucocytes were charted in their calculated absolute values and not their relative or percentage values.

Animals were classified as (I) *Normal*, or uninoculated controls; (II), *Acute*, which, by definition, were those which received an inoculation of tubercle bacilli that caused them to die of generalized tuberculosis in less than four months; and (III) *Chronic*, those animals that were inoculated with tubercle bacilli and at some time showed enlarged, palpable regional lymph nodes or in which tuberculous lesions were found at autopsy, but which did not die of tuberculosis in less than nine months. These three groups will be discussed separately.

STUDIES ON NORMAL ANIMALS

Seven normal animals were examined during the period of experiment, a total of 130 complete counts being made on them. Isolated counts were made on a score of other normal animals (see nos. 3 and 20, charts 1 and 2, and table 1). The following normal standard was established

for male guinea pigs, of from three months to two years of age and living in our laboratories.

These results approximate closely those obtained by other workers, as seen in the table in Burnett's *Clinical Pathology of the Blood of Animals*. The red blood count is there given as 5,276,000, Burnett (26); 5,859,000, Hayem (27); 5,780,000, Kurloff (28); and 4,240,000, Cohenstein and Zuntz (29). Burnett found a hemoglobin reading of 94.5 per cent. Leucocyte counts were 7,000, Bethe; 11,000, Burnett; 5,600, Hayem; and 12,600, Kurloff.

The differences between normal guinea pig and normal human blood are most noticeable in the higher red blood cell count and hemoglobin percentage and the markedly higher lymphocyte count in the guinea pig. There is also less variability in the erythrocyte and hemoglobin counts

TABLE 1

	PER CUBIC MILLIMETRE	PER CENT
Erythrocytes	6,000,000	
Hemoglobin		95
Leucocytes	10,000 to 15,000	
Lymphocytes	5,000 to 8,000	35 to 55
Large mononuclears	500 to 1,000	5 to 8
Transitionals	0 to 300	0 to 3
Neutrophiles	5,000 to 10,000	35 to 60
Eosinophiles	300 to 400	3 to 4
Basophiles	100	1

in guinea pigs than in man. The absolute lymphocyte count in the guinea pig is about equal to the total leucocyte count in man. It is interesting to note that the newborn guinea pig has a red blood cell count of 7,000,000, hemoglobin of 100 per cent, and leucocyte count of from 3,000 to 8,000 with only about 25 per cent lymphocytes (see table 2). *Thus the lymphocyte picture in infancy and maturity is completely reversed in man compared with the guinea pig.* This seems to be an important fact in view of the studies on immunity and resistance to tuberculosis. Thus, it is believed, and some experiments above quoted indicate, that the lymphocytes are an important factor in resistance to tuberculosis. Nevertheless, it is well known that the human infant and the guinea pig show particularly slight resistance to the infection.

The variations in the total leucocyte count were usually due to the neutrophilic polymorphonuclear cells and in the extreme cases were directly traceable to acute infections, particularly infected wounds of the

back received in fights. These are well seen in no. 20, chart 2, in the late summer of 1921. It was necessary to kill two of the animals as a result of these injuries. The acute infections were accompanied by a temporary drop in the red blood cell count and hemoglobin, with the appearance of nucleated erythrocytes.

TABLE 2

Leucocyte counts of newborn guinea pigs

ANIMAL	W.B.C.	LYMPHOCYTES	LARGE MONONUCLEARS	NEUTROPHILES	EOSINOPHILES	KURLOFF BODIES
		per cent	*per cent*	*per cent*	*per cent*	
94b	800	50	5	43	0	0
95b	3,000	40	12	48	0	0
98b	3,000	13	4	81	0	0
99b	4,500	34	4	60	1	0
100b	4,000	16	8	70	3	0
101b	8,000	10	6	84	0	0
102b		25	10	58	6	0
103b		14	7	80	1	0

TABLE 3

Seasonal variations in the color index of normal guinea pigs

ANIMAL	PERCENTAGE COLOR INDEX FOR			
	April, 1921	April, 1922	August, 1921	August, 1922
1	98	96	94	90
2	97	93	93	
3	105	96	95	90
19	101		88	
20	100	97	93	95
45		97		90
46		96		90
Average.....	100	96.5	92.5	91
Seasonal average.....	98.3		91.8	

Seasonal difference = 6.5 per cent.

N.B.: 100 per cent represents 6,000,000 R.B.C. and 95 per cent Hb.

With the exception of these periods of acute infections, the red blood counts held a fairly even course. It will be noted that the charts were made on the basis that 6,000,000 red blood cells and 95 per cent hemoglobin is 100 per cent normal. However, the hemoglobin curve frequently falls below that of the red blood cell curve. A very interesting seasonal variation is seen in this drop in hemoglobin relative to the

corpuscular count. The hemoglobin curve most closely approaches or exceeds the red blood cell curve in winter or early spring, and the divergence of the two is greatest in late summer. In other words, the color index is lower in summer than in winter (see table 3). This is even more clearly brought out in the animals with chronic tuberculosis, which will be discussed later. Might this not represent a physiological variation in oxidation and heat production to accommodate the different seasons? Recently Hess and Lundagen (30) have reported seasonal tides in blood phosphates in infants, which they believe to be due to similar tides in ultraviolet rays of the sunlight, since the infants have more phosphates during the summer or when exposed to the direct rays of the sun. Our guinea pigs are never exposed to the direct rays of the sun, so it is doubtful whether the variations in hemoglobin content of the individual blood corpuscles could be dependent on this factor. But we agree with Hess and Lundagen that the seasonal variation in the blood and other tissue activities justifies much further study.

Kurloff bodies: The eosinophile count was uniformly low in the early months of the investigation, after which there was a sudden and marked rise which was maintained for the rest of the time. Coincident with this eosinophilia, the so called Kurloff bodies were first noted in the cytoplasm of some of the large mononuclear (indicated by crosses on the large mononuclear curves in the charts). It has been our intention to make a rather careful study of these bodies, since we believe that reservations must be made on all conclusions drawn from hematological studies in guinea pigs, until these bodies are explained, more particularly because of the coincident eosinophilia found in our normal animals.

Many theories have been offered as to the nature and significance of these Kurloff bodies but none have as yet been satisfactorily proved.

1: Kurloff (28), who first noted them in 1888, was of the opinion that they were aggregations of the punctate granules of the cytoplasm of lymphocytes, and that, although these granules are common to the lymphocytes of many species, the aggregation of them in the form of these so called Kurloff bodies is peculiar to the guinea pig and related families. This theory is also held by Pappenheim and Ferrata (31) and Maximow (personal interview).

2: Schilling-Torgau (32), Patella (33) and Ledingham (34) suggest that they may be cell secretions reacting against toxins, body hormones or immune bodies.

3: It was believed by Ledig, Goldhorn (35) and Hunter (36) that they are intracellular protozoa, parasites, or *Chlamydozoa.*

4: Ross (37) offers evidence to prove that they are *Lymphocytozoa cobayae,* or spirochetes, related to the virus of human syphilis, in which the Kurloff body represents the intracellular stage in the life cycle, and he claimed that spirochetes are to be found free in the blood stream.

5: Woodcock (38) maintains that they are incompletely digested, phagocytosed red blood cells.

A detailed description, with many excellent colored plates, is given by Pappenheim and Ferrata (31).

We have studied these Kurloff bodies in connection with our work but are as yet undecided as to their nature. These studies will be continued, but the following preliminary report may be made:

1. The Kurloff bodies did not appear in the early months of our work. Many of these early smears had been preserved and were carefully reëxamined after the Kurloff bodies had been studied, and we were able to verify the fact that they had not been merely unrecognized and overlooked in the first examination. They were first noticed in large numbers in the blood of the animals in one particular cage, and then seemed to spread to all the surrounding cages, until all animals were found to possess them. All animals that have entered our laboratory subsequent to that time have had Kurloff bodies. They were found in guinea pigs examined in three other laboratories of the University, although rats, mice, and rabbits living under the same conditions had no intracellular bodies. The German worker, Pappenheim (39), reported that all guinea pigs in his experience had Kurloff bodies. Maximow (personal interview) claims that all the guinea pigs in Russia investigated by him had them. Ross (37) stated that 90 per cent of the guinea pigs of England were infected with his so called *Lymphocytozoa cobayae.*

2. While there had been an eosinophile count in normal animals at a normal level, never to exceed 4 per cent, previous to the appearance of the Kurloff bodies, coincident with their appearance the eosinophile counts of these animals immediately increased, frequently reaching a 30 per cent level. None of the other workers have noted any relation between the Kurloff bodies and eosinophiles, although several report a marked variability in the eosinophile count in supposedly normal animals. Burnett (26) found the eosinophiles of 17 animals, some of which had intracellular bodies, to vary from 1 to 20 per cent, but he suggests no relationship between the two facts. Maximow recognizes the

variability of the eosinophiles in guinea pigs but does not believe that it is related to the Kurloff bodies.

3. We found, as did Pappenheim (39), that the embryo and newborn guinea pigs do not possess Kurloff bodies, even though the mother has them in large numbers. We could not verify the fact, as suggested by Pappenheim, that pregnant animals had more Kurloff bodies than other animals. The Kurloff bodies appeared in the young guinea pigs between the second and third months of extrauterine life. These young animals had been left in the same cages with animals possessing the bodies. So far, efforts to transfuse blood from animals known to possess the intracellular inclusions into these young guinea pigs have failed, due, apparently, to the incompatibility of the blood, as the animals died immediately in shock. This work will be repeated.

4. We have failed to confirm the work of Woodcock (38), who believes that the Kurloff bodies represent phagocytosed red blood cells which the lymphocyte is unable to digest completely. All the technique suggested by Woodcock has been used repeatedly, as have been many other staining methods, but no iron stain for the Kurloff body was successful, nor did any other stain show any marked resemblance between the red blood cell and the Kurloff body. A lymphocyte in the process of ingesting a red blood cell has never been seen.

5. We have also been unable to confirm the work of Ross (37), who stated that he saw free spirochetes in the blood of animals possessing Kurloff bodies, and could trace a direct relation between the two. We studied the blood of many animals, and of each animal several times, with the dark field illuminator, and also examined emulsions of the liver, spleen, bone-marrow and testes with the dark field illuminator. Smears of the blood and organs were also made and stained with the long Giemsa method and with India ink. But in no instance was a spirochete ever seen, or any other microörganism free in the blood stream or in the organ emulsions. However, many irregular small scars were seen in the liver of two of the normal animals (nos. 45 and 46). Microscopic studies revealed small areas of necrosis beneath the capsule, at points where the capsule was drawn in and the endothelial cells of the capsule had assumed a cuboidal shape. There was no fibrosis. Small areas of round cells appeared irregularly throughout the liver. They were not perivascular. Ross reported this condition also and thought the lesions were gummata. He also thought that a slight anemia was caused by the Kurloff bodies.

6. Blood smears containing Kurloff bodies and stained with Wright's and Giemsa stains were submitted to Dr. E. E. Tyzzer of Harvard University and Dr. B. H. Willier of the University of Chicago, and each stated independently that there was no definite evidence that the Kurloff body was any known parasite.

7. We have found that new methylene blue *G.G.*, used as a supravital stain, is specific for Kurloff bodies and is the best way of identifying them. They invariably take on a brilliant cherry red, while the cytoplasm and nucleus of the cell, containing the inclusion, and all other cells of the blood are blue, except that in certain concentrations a varying degree of a reddish hue may be acquired by the basophile granules which cannot be confused with a Kurloff body. Related dyes, such as capri blue and Nile blue, do not give the same results.

The following tentative conclusions may be drawn:

1. The nature and significance of the Kurloff body is still uncertain and the subject requires further study.

2. Their possible relationship to the variable eosinophile count makes it impossible to draw any conclusions about experimental eosinophilia in animals possessing Kurloff bodies.

3. They may possibly be associated with small, irregular scars in the liver and with a mild anemia, and thus help to confuse the picture of experimental tuberculosis.

STUDIES ON ANIMALS WITH ACUTE EXPERIMENTAL TUBERCULOSIS

An acute infection was developed in guinea pigs that were heavily inoculated. They usually died of generalized tuberculosis in less than four months. Autopsies of them revealed the usual picture of generalized tuberculosis of lymph nodes, spleen, lungs and liver. There was a rapid loss of weight before death. Fourteen animals of this type were examined after inoculation until death. One hundred and forty complete counts were made (see nos. 6 and 26, chart 1, 28, 29, and 36, chart 2 and chart 3). Charts of these examinations show very typical curves for the blood in acute generalized experimental tuberculosis. The anemia progresses rapidly, the erythrocytes frequently decreasing steadily, with relatively few variations, to 3,500,000. Nucleated erythrocytes were seen only three times, and then not to exceed 3 per 100 leucocytes. The hemoglobin dropped much more rapidly than the red blood cells,

falling at times to 35 per cent. The leucocyte count was more variable, but the greatest variations were due to the neutrophilic polymorphonuclear leucocytes. At termination, either a leucocytosis or a leucopenia might be shown. The leucopenia, when present, was more marked than the leucocytosis; counts below 7,000 being seen in animals 23, 26, 28 and 38. The leucocytosis might be considered as signifying a terminal secondary infection, but there was no demonstrable pathological difference between the animals dying with leucopenia and those dying with leucocytosis. Even when the leucocytosis was between 20,000 and 30,000, as in animals, 5, 7, 35, 36 and 39, it was entirely due to the neutrophilic polymorphonuclear cells.

The lymphocytes persistently decreased until death, and there was never any indication of an increased lymphocyte count; at death they were frequently one-fifth to one-tenth that of normal animals. A preterminal increase of lymphocytes in one animal, to almost 8,000 is an exception that we cannot explain. At any rate, it does not represent, apparently, an increased resistance. The large mononuclear and transitional cells show a preterminal increase to about double. They may stay at this level until death, or again decrease to normal or below. McJunkin (24) recognized such an increase in what he called endothelial cells, and thought they might indicate a last desperate effort on the part of the body to develop a resistance to the disease, but he was unable to demonstrate any increased resistance to tuberculosis in animals in which he induced an artificial endothelial leucocytosis. We are not sure that our large mononuclear and transitional cells are all identical with McJunkin's endothelial cells, although Sabin (40) has recently brought forward evidence to show that what are generally large mononuclear and transitional cells are of endothelial origin. There was no evidence in our work that this late increase in the large mononuclear elements increased the resistance of the animal. On the other hand, it might be suggested that their increase represents a final breakdown of the body, since death follows always within a few days, and that they may arise from the endothelium of the badly injured spleen and liver.

Eosinophiles were decreased or absent in all but one case (no. 36, chart 2). This animal had an eosinophilia of from 4 per cent to 7 per cent and lived longer than any other acute case. Kurloff bodies were never noted in any of these cases.

When the guinea pig died of some acute infection, such as peritonitis, the blood picture looked as though it had been left uncompleted, when compared to that of animals that died of generalized tuberculosis.

Chart 3 is of particular interest, as it shows 3 guinea pigs in presumably the same condition, given the same inoculation of the tubercle bacilli at the same time and yet with very different blood pictures. Case 5 really belongs to the type of chronic tuberculosis and will be discussed with the other chronic cases. This chart shows that the more rapid and acute the tuberculous process the more marked are the blood changes. This is particularly true of the tuberculous anemia, that is, the decreases in the red blood cells and their hemoglobin content, and of the lymphocytes. Autopsies showed that the animal which died first had the most extensive tuberculous lesions and the one that died last the least.

It may be concluded that in acute experimental tuberculosis of the guinea pig, a prognosis of the disease may be fairly easily made from the progress of the blood picture, unless the life of the animal is cut short by some acute secondary infection.

STUDIES ON ANIMALS WITH CHRONIC EXPERIMENTAL TUBERCULOSIS

A chronic infection developed in animals which received relatively light inoculations and showed a prolonged resistance to the disease (see nos. 8, chart 1, 14, chart 2 and 5, chart 3). These animals lived nine months or more after inoculation and frequently died of conditions other than tuberculosis, especially pneumonia, and never showed at autopsy tuberculous lesions as extensive as those in the acute cases. In some cases, in fact, no macroscopic lesions were found at death twelve to fourteen months after inoculation, although enlarged regional lymph nodes had at various times been palpated and these had later discharged through ulcers at the point of inoculation; also with these the blood pictures varied considerably from those of the uninoculated animals, resembling those of the other animals with chronic tuberculosis.

Thirteen animals with chronic tuberculosis were examined, a total of 350 complete blood counts being made. The most striking phenomena in the blood charts of chronic tuberculosis are the marked fluctuations of all the elements. These fluctuations are seen in the erythrocytes and their hemoglobin content, the total leucocyte counts and the individual leucocyte cells, such as the neutrophiles, lymphocytes and eosinophiles. There seems to be a tendency for all the elements to fluctuate together in the larger variations, although smaller variations in the individual elements occur by themselves. There are also undoubtedly other factors at work on the blood picture, such as leucocytic reactions to secondary infections, eosinophilia, etc. But, allowing for such factors, the blood

picture suggests the possibility that the variations are not due to absolute increases and decreases in the cells of the blood, but to relative changes due to variations in the blood concentration or plasma content of the blood. As the guinea pigs did not have hemoptysis, night sweats or diarrhea, this apparent change in blood concentration cannot be caused by these factors, as assumed in clinical work, but must be related to some such factor as that suggested by the work of Gaertner and Roemer (18), who showed that the products of tubercle bacilli cause an increased lymph flow in dogs. We believe this marked fluctuation to be the most significant part of the blood picture in chronic tuberculosis, and one that demands further study and consideration, not only to determine the underlying causes, whether these be a secretagogue action of the products of the infection or lesions, changes in the permeability of the blood capillaries, or changes in the osmotic pressure of the blood; but also because the fluctuation explains the great diversity of opinion as to the blood changes that occur in tuberculosis, especially when conclusions are drawn from one count or a few isolated counts on each patient; and it also indicates the futility of attempting to make a diagnosis from one blood count.

We are now engaged in carrying on some experiments, adapted to the living guinea pig, on the variability of the blood concentration of similar tuberculous animals.

A more careful analysis of the charts of these chronic tuberculous animals brings out certain other points:

1. The animals never showed the blood picture characteristic of acute tuberculosis, not even at termination. It is just as likely that the animal will die at a high peak of cellular count, including erythrocytes and hemoglobin (see nos. 5 and 8).

2. There is a characteristic chlorotoid anemia, not, however, as marked as that seen toward the end in acute tuberculosis. This is apparently not progressive, for if allowances be made for the seasonal variations in the hemoglobin content of the red blood cells, it will be seen that after the first few months of the disease the erythrocyte curve and the hemoglobin curve are roughly parallel. The seasonal variation is clearly seen, however (see table 4). Thus, the seasonal difference in the color index between April and August averaged 10.3 per cent for chronic tuberculosis, as compared to 6.5 per cent for normal animals. Nucleated erythrocytes were never seen.

3. The least variations are seen in the mononuclear elements. There is not a progressive decrease in the lymphocytes as seen in the acute cases; the lymphocytes were never unusually low, even as the end approached, with the autopsy indicating death from tuberculosis. On the other hand, with the exception of the one isolated count of case 14, the lymphocytes never exceeded the normal absolute value. There was never a temporary or prolonged lymphocytosis, even in animals living almost two years after inoculation and then very few tuberculous lesions. We thus obtained no evidence to indicate that resistance to tuberculosis is maintained by the lymphocytes. Of course, it is possible that the more circumscribed lesion of the reinfections

TABLE 4

Seasonal variations in the color index of guinea pigs with chronic tuberculosis

ANIMAL	PERCENTAGE COLOR INDEX FOR			
	April, 1921	April, 1922	August, 1921	August, 1922
7	103	101	83	82
8	95	92	88	77
9	99	94	77	86
10	85	88	82	89
11	96		82	
12	103	93	85	86
14	87	85	83	
Average.....	95.4	92.2	82.9	84
Seasonal average.....	93.8		83.5	

Seasonal difference = 10.3 per cent.

N.B.: 100 per cent represents 6,000,000 R.B.C. and 95 per cent Hb.

of adult human tuberculosis stimulates the production of a lymphocytosis, when the amount of systemic intoxication is undoubtedly much smaller than that of the marked generalized tuberculosis of our acutely infected, and probably even of the chronic infected, nonsensitized guinea pigs, in which the lesions tend to be destructive rather than proliferative. Nevertheless, it is interesting to note W. J. Mayo's (41) recent suggestion that the lymphatic system is a point of weakness in the body, in which such diseases as cancer, syphilis, and tuberculosis are concerned, rather than a point of strength as is usually assumed. Attention should again be called to the fact that the guinea pig, like the human infant, has a very high percentage of lymphocytes and a relatively low resistance to tuberculous infection. It would be worth while to determine the resistance of the

newborn guinea pig, which has a low lymphocyte count similar to that of the human adult. This has apparently not been done. Experiments (42) indicating that stimulation of lymphoid tissue increases resistance to tuberculosis and vice versa (21) have been questioned by more recent work (22). While the assumption that resistance to clinical tuberculosis is associated with a lymphocytosis is based on such work as that of Webb, Gilbert and Newman (43), Cummings (15), who studied the lymphocytes in 100 patients with tuberculosis and in 40 normal individuals, found an average of 30.5 per cent lymphocytes for the normal individuals, 27.4 per cent for tuberculous cases of good prognosis, and 16 per cent for those of bad prognosis and believed that "a high percentage of lymphocytes was indicative of increased resistance." But even in those cases of good prognosis the percentage is below normal. Moreover, these are percentage and not absolute figures, and their value depends largely upon the polymorphonuclear counts which vary more markedly in open cases of pulmonary tuberculosis than do the lymphocytes.

4. The eosinophiles in all our chronic cases held a high level (except for case 5). As the animals of one group had all been studied and had died before we first observed Kurloff bodies, we were of the opinion that this marked eosinophilia was an indication of increased resistance to the infection, more especially as neither the normal animals nor the acute cases examined over the same period showed any eosinophilia. However, all following cases showed both Kurloff bodies and eosinophilia, and the tracings were very similar to those of the normal animals after Kurloff bodies were noticed in their blood. Therefore, no certain conclusions about the eosinophilia can be drawn at present.

Thus, the blood picture in chronic tuberculosis is characterized by marked fluctuations in all elements, a nonprogressive chlorotoid anemia, an absence in lymphocytic reaction and a possible eosinophilia.

COAGULATION TIME

Tests of the coagulability of the blood were not made in the first part of the investigation. They were begun in November, 1921 (see chart 4). The Boggs coagulometer was employed. A total of 200 tests were made, 70 on 5 normal animals, 30 in 5 cases of acute tuberculosis, and 100 in 7 cases of chronic tuberculosis. An average time of about five minutes, with variations between four and five and one-half minutes, was obtained for the normal animals. This decreased a little, to about four or four and

one-half minutes, as the guinea pigs increased in age. The animals with chronic tuberculosis showed very little variation from this; although the progressive shortening of the time with increasing age seemed a little more marked, falling to about three and one-half minutes. But a very marked decrease in coagulability was noted in the animals with acute tuberculosis, the time being about doubled just previous to death. This may be associated with the marked liver injury which was always present in such cases. It is interesting, in this connection, to find that the doubling of the number of endothelial cells, before mentioned, occurs at the same time with the high peak of the coagulation time, while both phenomena are absent in the chronic cases.

No previous work on the coagulation time in experimental tuberculosis has been reported. For human tuberculosis Galera (44) records a retarded coagulation, due, he believed, to the scarcity of blood calcium. Solis-Cohen (45) reports a shortened clotting time associated with hemoptysis. Burns and Young (46) found no striking relation between the coagulation time and hemoptysis. Rudolph and Cole (47) found the average normal time to be seven minutes, while the average time for 9 cases in all stages of pulmonary tuberculosis was 8.9 minutes. Halverson, *et al.*, (48), showed that there is no marked deviation in the calcium content of the blood in patients in the various stages of tuberculosis. The guinea pigs did not have hemoptysis; so the cause for the retardation in the coagulability in our acute cases must be sought for elsewhere, possibly in the hepatic lesions.

ARNETH COUNTS

Sixty-four Arneth counts were made on 28 animals; 12 counts being made on 7 normal animals, 18 counts on 10 acute cases of tuberculosis, and 34 counts on 11 chronic cases (see table 5). When starting these examinations we were unable to find any references to previous work on the Arneth count in experimental tuberculosis, and in studying the blood of normal guinea pigs, compared to normal human blood, the conclusion was drawn that the leucocytes of the guinea pig had a relatively larger number of nuclear parts than the leucocytes of man. Thus, 7 groups were made and the majority of cells were thought to belong to groups 4 and 5, while Arneth (49) placed human blood in 5 groups with the majority of cells in groups 2 and 3.

TABLE 5
Arneth index

ANIMAL	DATE OF EXAMINATION	NUMBER OF NUCLEAR PARTS PER 100 CELLS	NUMBER OF NEUTROPHILES PER CUBIC MILLIMETRE OF BLOOD	DATE OF DEATH
		Normal animals		
1	2/13/22	443	4,800	
2	8/29/21	417	6,200	
3	10/ 8/21	401	6,100	
	4/15/22	422	2,900	
	5/17/22	454	3,700	
20	2/13/22	437	9,200	
19	8/22/21	336 (Acute infection)	1,900	
45	1/13/22	489	6,000	
	2/14/22	437	6,700	
	3/22/22	476	6,200	
46	2/13/22	502	6,700	
	3/13/22	504	4,600	
Average.....		448	6,300	
		Chronic tuberculosis		
5	9/22/21	414	4,100	
	10/10/21	334	5,800	1/ 2/22
7	2/ 8/22	422	10,300	
	3/ 9/22	415	6,200	
	5/29/22	439	7,800	
	8/ 2/22	421	7,300	9/ 5/22
8	1/ 6/22	431	5,100	
	2/ 8/22	412	8,400	
	3/ 9/22	419	6,200	
	4/ 5/22	404	10,100	
	5/29/22	422	7,000	
	10/12/22	412	10,700	10/18/22
9	2/ 8/22	444	8,800	
	3/ 5/22	427	13,600	
	8/ 3/22	461	6,900	
	10/11/22	462	12,800	
10	2/10/22	416	7,400	
	3/10/22	484	8,000	
	5/17/22	472	7,000	12/25/22
11	2/ 8/22	474	8,300	
	3/11/22	427	4,100	4/14/22
12	3/13/22	426	10,700	
	10/12/22	434	5,900	11/25/22
14	8/18/21	400	4,800	
	2/11/22	447	18,600	
	3/22/22	424	15,100	

TABLE 5—*Continued*

ANIMAL	DATE OF EXAMINATION	NUMBER OF NUCLEAR PARTS PER 100 CELLS	NUMBER OF NEUTROPHILES PER CUBIC MILLIMETRE OF BLOOD	DATE OF DEATH
		Chronic tuberculosis—Continued		
	5/16/22	402	15,400	
	6/22/21	325	8,200	7/26/22
17	8/23/21	402	13,800	
	9/21/21	409	22,800	11/ 2/21
41	10/10/22	422	6,200	
42	3/ 7/22	450	6,000	
	8/23/22	421	7,400	
	10/10/22	433	5,500	12/23/22
Average.....		426	9,000	
		Acute tuberculosis		
6	7/19/21	406	11,800	8/12/21
23	8/11/21	328	4,600	8/11/21
26	8/31/21	329	3,600	
	9/ 5/21	276	1,100	9/ 7/21
27	7/27/21	350	7,000	
	7/28/21	363	7,200	7/28/21
28	8/11/21	316	2,300	8/11/21
29	8/19/21	387	5,400	
	9/27/21	355	7,400	10/ 3/22
31	8/31/21	405	5,800	
	10/ 7/21	405	14,400	10/17/22
36	1/28/22	401	15,400	
	3/ 2/22	406	13,300	
	3/10/22	424	17,700	3/13/22
40	4/ 1/22	409	4,800	
	5/ 1/22	389	6,700	
	6/ 7/22	377	4,500	6/23/22
14	6/22/22	325	8,200	7/26/22
Average.....		342	7,700	

After completing our work we found a paper by Treadgold (50). He had determined a normal standard for guinea pigs on apparently the same basis as Arneth's work on man. In our work we have used the method suggested by von Bonsdorf (51), of adding all the nuclear parts of 100 polymorphonuclear cells together, and thus obtaining one figure representing the total nuclear parts per 100 leucocytes. This is much simpler than the Arneth-index picture. Thus, a decrease in nuclear parts per 100 cells represents Arneth's "shift to the left." Treadgold

also expressed his results in nuclear parts per 100 cells, and determined an average number of 267 in 5 normal guinea pigs while our average figure was 448. This indicates one of the greatest disadvantages of the Arneth count, which is the inability to standardize the counts, as no two persons interpret the nuclear parts in the same way. Treadgold then followed the process of tuberculosis in 3 inoculated guinea pigs and found a primary "shift to the right," or increase in nuclear parts, lasting from one to ten days and followed by a "shift to the left," or progressive decrease in nuclear parts, until death, when the indices were 204, 181 and 174. The table of our results shows an average of 448 nuclear parts per 100 cells in normal animals, of 426 in chronic tuberculosis, and 342 in acute tuberculosis. This decrease represents a "shift to the left." There are, however, certain conspicuous inconsistencies in the Arneth counts that are not easy to explain. Thus, about one-half of the normal counts are below the average for chronic tuberculosis, and about one-sixth of the chronic cases are above the average for normal animals. These latter might be explained on the basis of the "shift to the right" observed by Treadgold in his tuberculous animals. One of the normal animals had an acute secondary infection at the time the low Arneth count was observed, but the other cases are not so easily accounted for.

It was thought by Arneth that the "shift to the left" indicated that there was an increased demand on the bone-marrow for leucocytes, so that they were rushed into the blood stream before they were fully matured, and that the cells with the small number of nuclear parts represent young and inefficient cells. From our table it appears that this idea is borne out in part. Thus, the normal animals had the smallest number of neutrophilic polymorphonuclear cells per unit of blood and the largest number of nuclear parts per 100 cells, and in tuberculosis the number of cells increased while their nuclear parts decreased. However, the number of cells is less in the acute than in the chronic cases, while the nuclear parts are still decreasing. If, however, the Arneth counts are placed in three groups, based entirely on the value of the number of nuclear parts per 100 cells, we find that the average number of neutrophilic cells per unit of blood, in specimens having less than 350 nuclear parts per 100 cells, is 5,700; while there was an average of 6,400 neutrophiles in specimens having from 350 to 400 nuclear parts per 100 cells and an average of 9,300 neutrophiles in specimens having above 400 nuclear parts per 100 cells. This shows, then, that in our animals the large number and not the reduced number of nuclear parts is present in a leucocytosis.

An interesting relation exists between the anemia of the animal and the Arneth index. This is illustrated in chart 5, of case 14, which shows that the number of neutrophilic cells per unit of blood, the number of nuclear parts per 100 cells and the percentage of hemoglobin tend to rise and fall together.

CONCLUSIONS

1. Normal guinea pigs have a very uniform blood picture, particularly characterized by a seasonal variation of the hemoglobin content of the red blood cells, a high lymphocyte count and a high eosinophile count coincident with the appearance of Kurloff bodies. The newborn guinea pig has a low lymphocyte count.

2. An acute infection with tuberculosis produces a characteristic blood picture, in which there is a rapid loss in erythrocytes with a relatively greater decrease in hemoglobin, a terminal leucocytosis or leucopenia, a progressive decrease in lymphocytes, a marked preterminal increase in endothelial cells and an absence of eosinophiles.

3. Chronic tuberculosis produces a blood picture quite different from that of acute tuberculosis. It is characterized by a marked fluctuation in all elements, a relatively low hemoglobin content of the erythrocytes, which is not progressive but shows the normal seasonal variations, an absence of any reaction in the lymphocytes, and an eosinophilia which cannot, however, be distinguished from that associated with Kurloff bodies.

4. The nature of the Kurloff bodies and their effects on the guinea pig are still undetermined, and, until they are better understood, definite conclusions cannot be drawn from hematological studies on the guinea pig.

5. The coagulability of the blood in chronic tuberculosis shows slight changes from the normal, but in acute tuberculosis it is markedly retarded.

6. The Arneth counts show a decrease in nuclear parts per 100 cells in tuberculosis, which, on the average, is greater in acute than in chronic cases but there are individual exceptions.

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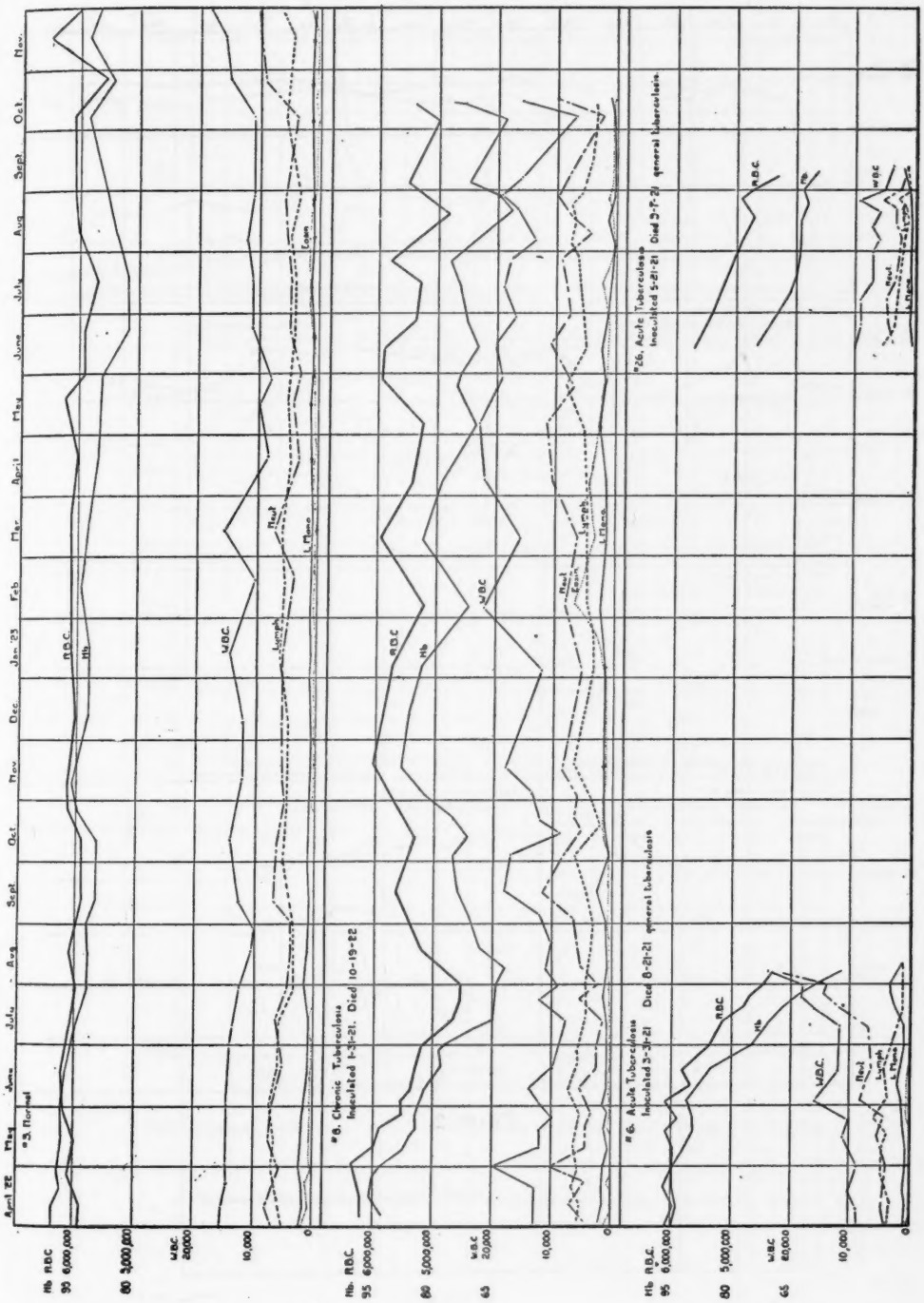
April 25
May
June
July
Aug
Sept
Oct
Nov
Dec
Jan 23
Feb
Mar
April
May
June
July
Aug
Sept
Oct
Nov
#3. Normal
#8. Chronic Tuberculosis
Inoculated 1-31-21. Died 10-19-22
#6. Acute Tuberculosis
Inoculated 3-31-21 Died 8-21-21 general tuberculosis
#26. Acute Tuberculosis
Inoculated 5-21-21 Died 3-9-23 general tuberculosis
Hb
R.B.C.
W.B.C.
Neut.
Lymph.
Mono.
Eosin.
Baso.

CHART 1

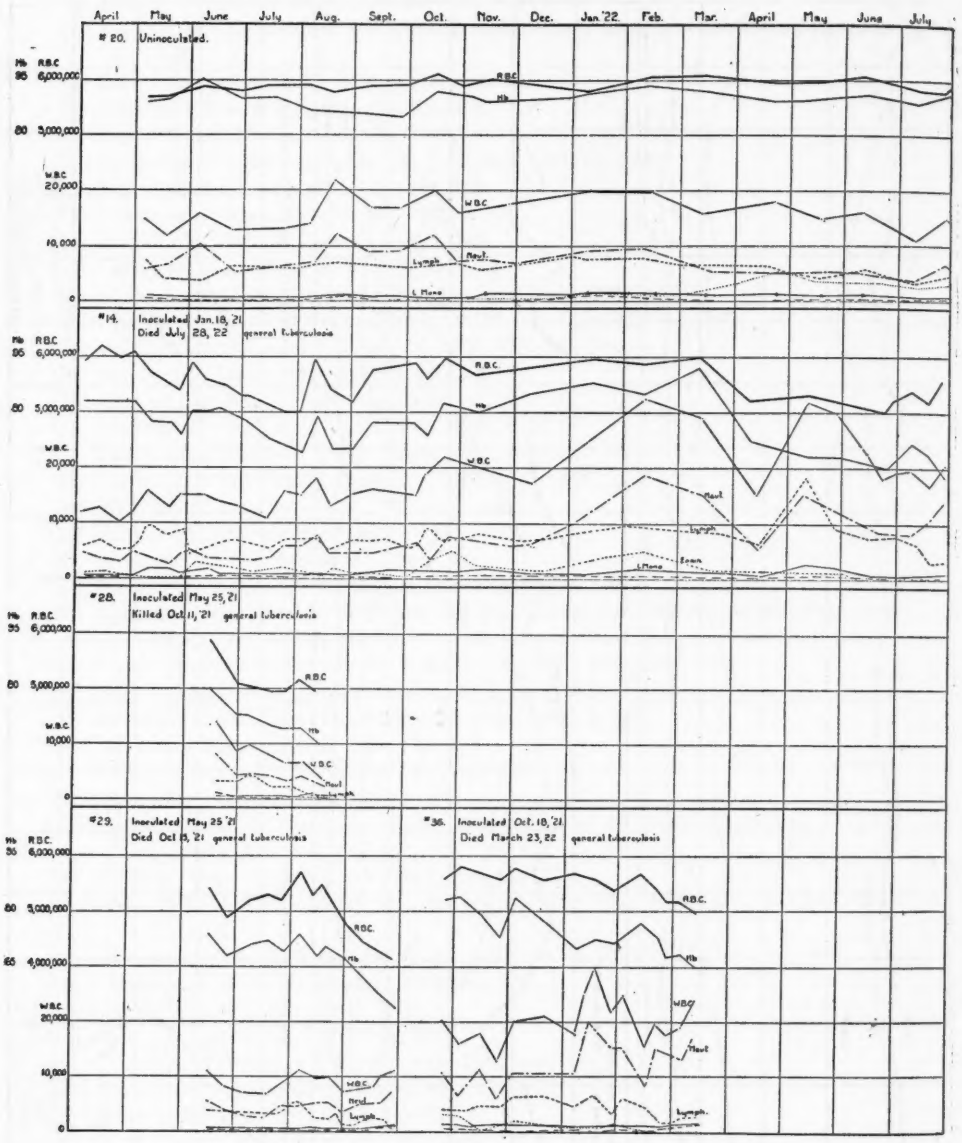
April
May
June
July
Aug.
Sept.
Oct.
Nov.
Dec.
Jan. '22
Feb.
Mar.
April
May
June
July
20. Uninoculated.
Hb
R.B.C.
95
6,000,000
80
5,000,000
W.B.C.
20,000
10,000
0
RBC
Hb
WBC
Lymph
Neut.
L. Mono
#14. Inoculated Jan. 18, 21
Died July 28, 22 general tuberculosis
Eosin
#28. Inoculated May 25, '21
Killed Oct. 11, '21 general tuberculosis
#29. Inoculated May 25 '21
Died Oct 9, '21 general tuberculosis
65
4,000,000
#36. Inoculated Oct. 18, '21
Died March 23, 22 general tuberculosis

CHART 2

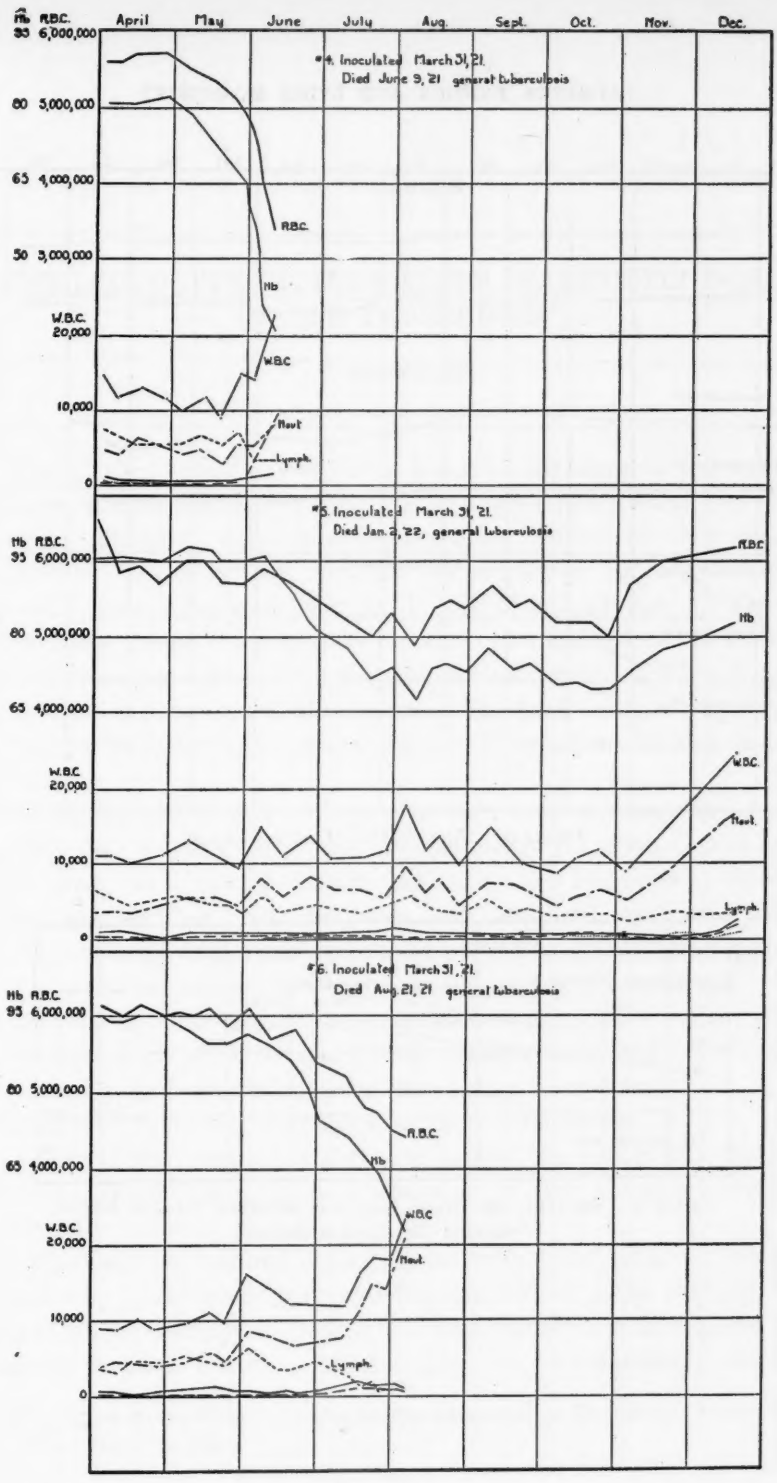
April
May
June
July
Aug.
Sept.
Oct.
Nov.
Dec.
Hb R.B.C.
95 6,000,000
80 5,000,000
65 4,000,000
50 3,000,000
W.B.C.
20,000
10,000
0
#4. Inoculated March 31, 21.
Died June 9, 21 general tuberculosis
R.B.C.
Hb
W.B.C.
Neut.
Lymph.
#5. Inoculated March 31, '21.
Died Jan. 2, '22, general tuberculosis
#6. Inoculated March 31, 21.
Died Aug. 21, 21 general tuberculosis

CHART 3

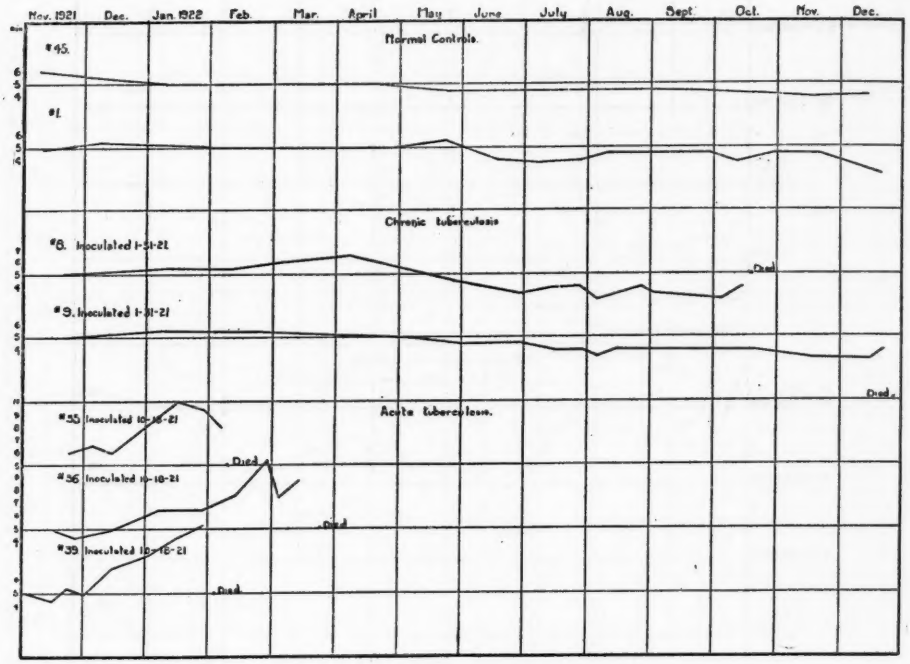

CHART 4. COAGULATION TIME OF BLOOD

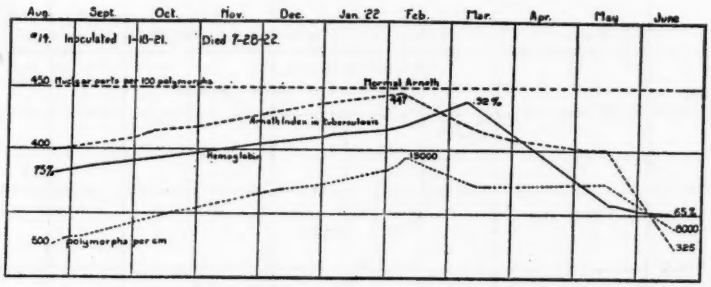

CHART 5. SHOWING THE CLOSE RELATION BETWEEN ARNETH INDEX, ANEMIA AND LEUCOCYTOSIS

THE LEUCOCYTE PICTURE AFTER DIAGNOSTIC DOSES OF OLD TUBERCULIN[1]

R. McBRAYER

Shelby, North Carolina

Having failed to find any report in American literature on this subject, we have studied 25 cases during the last three years while they were receiving diagnostic doses of old tuberculin. Fifteen of these reacted positively. The following method was employed: Each patient received, at forty-eight-hour intervals, 1, 3, 5, 10 and 10 mgm. O. T., subcutaneously, except the positively reacting cases which received no more after the reacting dose. A reacting case was so considered when it manifested local, general and focal reactions. The focal reaction was demonstrated by physical signs or stereoscopic X-ray films, though usually by both.

The leucocyte and differential counts were properly controlled before the first dose of tuberculin was administered. All other counts were made fifteen to eighteen hours after administration and midway between meals. No division of lymphocytes into large and small was made, because the large ones never exceeded 5 per cent. In the following tabulation, we have considered 500 or more cells an increase or decrease from the control, and a change of 5 per cent or more in the differential picture as a variation, except in the case of eosinophiles and basophiles, when we considered a 3 per cent increase or decrease as a variation.

Tabulation by cases, or analysis, shows the following:

Analysis of the following table warrants only the conclusion that the differential count is of no value or assistance in interpreting a borderline or definitely positively or negatively reacting case.

In the positively reacting cases, the leucocyte count, as a rule, slightly increased up to the count just preceding and following the reacting dose when it fell an average of 1000 cells. One might have anticipated this from the probable nature of the reaction. In the negatively reacting

[1] From the laboratory of the North Carolina Sanatorium for the Treatment of Tuberculosis, Sanatorium, North Carolina.

cases the count remained practically unchanged throughout, though with a general tendency to be about 500 cells below the control counts, though two cases constantly remained 300 to 600 cells above.

		INCREASED	DECREASED	UNCHANGED
		per cent	*per cent*	*per cent*
W. B. C.	Positively reacting cases	25	33	42
	Negatively reacting cases	30	43	27
Polymorphonuclears	Positively reacting cases	50	17	33
	Negatively reacting cases	22	23	55
Lymphocytes	Positively reacting cases	15	37	48
	Negatively reacting cases	17	42	41
Mononuclears	Positively reacting cases	7	15	78
	Negatively reacting cases	10	8	82
Transitionals	Positively reacting cases	5	1.6	93.4
	Negatively reacting cases	1.6	7	91.4
Eosinophiles	Positively reacting cases	8	23	69
	Negatively reacting cases	12	10	78
Basophiles	Positively reacting cases	3	0	97
	Negatively reacting cases	1.7	0	98.3

The eosinophile percentages in this report cannot be considered, because one negative and one positive case had a definite history of very recent asthmatic attacks and one case of each group had just been treated for clinically demonstrated hookworm disease.

CONCLUSIONS

In cases positively reacting to diagnostic doses of old tuberculin there is, as a rule, an appreciable drop in the leucocyte count. Otherwise, there is no certain or consistent leucocytic change. This laboratory procedure is therefore of no appreciable value to the clinician in the interpretation of his reactions.

THE ISOLATION AND CULTIVATION OF TUBERCLE BACILLI PROTECTED FROM LIGHT[1,2]

JAMES S. SIMMONS[3]

Since the work of Downs and Blunt in 1877 (1) abundant proof has accumulated on the powerful bactericidal action of light (Freund (2)). Degrees of illumination, not sufficient to kill bacteria, may inhibit the natural formation of pigment, the production of odors or the maintenance of normal virulence. The photochemical effect of light is due mainly to the action of the more refrangible, shortwaved, blue-violet and ultra-violet rays. The red rays exert practically no inhibiting effect on living matter. The action of direct sunlight is more powerful than that of diffuse daylight; but it is weaker than that of the light from an arc or electric spark.

Most authorities agree that cultures of tubercle bacilli are killed after exposures to direct sunlight of from several minutes to two hours, after several days' exposure to diffuse daylight, and in shorter time by lights giving off more of the chemical rays. Tubercle bacilli in sputum, or other materials, will stand longer exposures to light, depending upon the ability of the mucus and other substances present to protect them from chemical light rays.

In 1907 Weinzirl (3) found that tubercle bacilli placed upon glass or paper and exposed directly, that is, without glass or other cover, to the sun's rays, were killed in from two to ten minutes. Longer periods were required if the bacilli were clumped or bunched. His experiments showed that "so far as *B. tuberculosis* is concerned, it is the more refrangible rays, the violet end of the spectrum, which are bactericidal for this organism." In one of Weinzirl's experiments in which tubercle bacilli, placed on paper and covered with glass plates of various colors, were exposed to sunlight, he found that red plates protected the bacilli against exposure for a longer period than did plates of other colors. However, Weinzirl obtained "no growth" after thirty minutes' exposure of cultures, even

[1] From the Laboratory Service, Fitzsimmons General Hospital, Denver, Colorado.

[2] Approved for publication by the Surgeon General, U. S. A.

[3] Major, M. C., U. S. A.

under red plates, while by the red tube method, described below, cultures were living after more than three weeks of daily exposures to direct sunlight. As his technique is not given in detail, the kind of red color used and the completeness with which his cultures were covered by the red plates are not known.

The findings of various investigators show that in certain instances cultures of tubercle bacilli may undergo a loss of virulence. It has been suggested that this reported attenuation of tubercle bacilli after artificial cultivation might be caused by accidental exposure to light. Concerning this attentuation Cobbett (4) states

> If this is so the experience of the Commission (British Royal Commission of Tuberculosis, 1910) would seem to suggest that this loss does not depend simply on adaptation to the conditions of saprophytic existence, and a parallel loss of correspondence with a parasitic environment, but rather on some adventitious or accidental condition. For attenuation, when it takes place, seems to be irregular and capricious; and the suggestion naturally occurs that it may perhaps be caused by some such circumstance as unintentional exposure to diffuse daylight—or possibly even to the direct rays of the sun—on the laboratory bench when the cultures are being examined or resown, or to partial drying of the media, to resowing at too long intervals, or to some imperfection in the culture medium.

Corper (5) placed massive, full-grown cultures of virulent human tubercle bacilli in an incubator at 37.5°C. and exposed them to the light of an eight-candle-power carbon filament electric bulb, 6 to 8 inches from the culture tube. He found that after two days' exposure the culture was so affected that even 1 mgm. of the bacilli failed to infect guinea pigs, whereas, before exposure, 0.0001 mgm. produced a generalized infection within two months, when injected subcutaneously.

Red glass, which prevents the passage of most of the chemical light rays, allows only the red and infrared to pass through. Cultures of virulent human tubercle bacilli, grown in glass tubes coated outside with a red transparent paint, were still living after daily exposure to direct sunlight for three weeks. Control cultures of similar strains, in ordinary test tubes, exposed at the same time as the red tubes shown in figure 1, were killed in a few minutes.

In order to obtain, for experimental purposes, strains of tubercle bacilli which have not been exposed to the chemical rays of light, the following method may be used:

All glassware is covered with a thin coating of transparent, red paint. This may be prepared by mixing red aniline dyes with bleached shellac or a collodion base. However, the paint used in these studies was a commercial product (*Crescent*, Valparaiso, Indiana), sold for coloring electric light globes. This material dries very quickly, forming a thin, uniform, transparent, red layer over the glass; and is not affected by prolonged incubation at 37.5°C. The preparation does not interfere with careful observation of the cultures, which can be studied as easily in tubes thus coated as in uncoated tubes.

FIG. 1

Tube I. Culture of human tubercle bacilli on 4 per cent glycerine-agar, exposed to sunlight daily for three weeks. The bacilli were killed during the first few minutes of exposure.

Transplant I. Culture on Petroff's medium, by transfer from *Tube I* at the end of three weeks. There is no growth.

Tube II. Culture of human tubercle bacilli, similar to that in *Tube I*, but in a red-coated tube exposed to direct sunlight daily for three weeks.

Transplant II. Culture on Petroff's medium, by transfer from *Tube II* at the end of three weeks' exposure to sunlight. There is massive growth.

After cleansing the patient's mouth, tuberculous sputum is collected in sterile, red petri dishes or red glass bottles, and the material may then be treated by any of the isolation methods, using the red glass containers for each step. For instance, with Petroff's method, which is used here, the mixture of sputum and 3 per cent sodium hydroxide is placed in a red centrifuge tube and the sediment planted on Petroff's media in red coated tubes; after which it is incubated for the required period of time.

The powerful sunshine in high altitudes makes a method of this type desirable, especially in experimental studies, to rule out any influences which may injure the physicochemical composition or virulence of the bacillus.

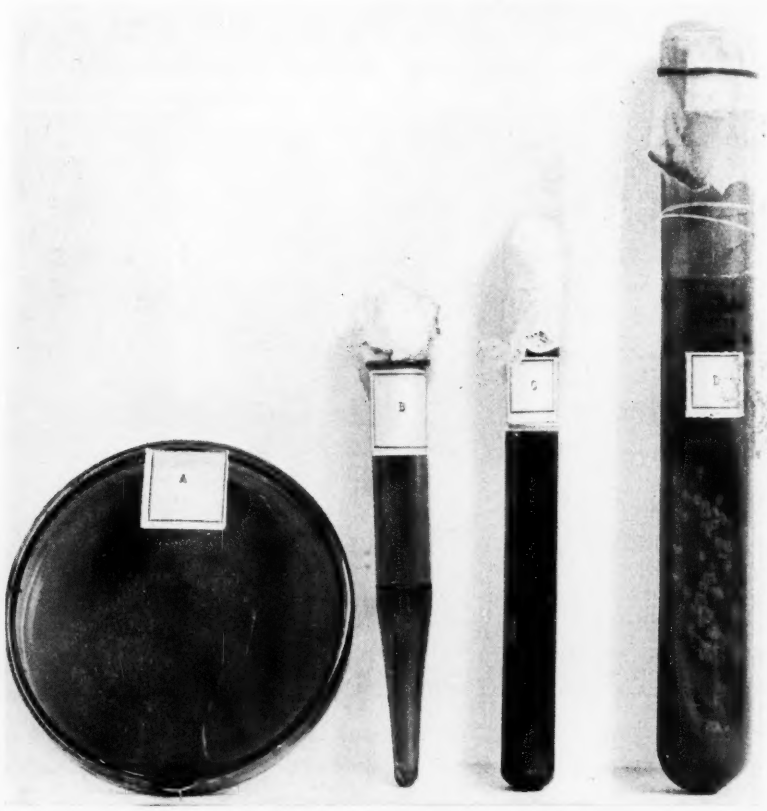

FIG. 2

A. Red-coated petri dish for collection of sputum, to obviate effect of light on tubercle bacilli.

B. Red-coated centrifuge tube for treatment of sputum with sodium hydrate preparatory to cultivation.

C. Red-coated tube of Petroff's medium for isolation of tubercle bacilli. Small size used to save incubator space.

D. Red-coated transplant tube. Large size for obtaining massive stock cultures.

After primary cultures are obtained, transplants may be made on glycerin-agar or any other medium desired, in red tubes, thereby keeping the particular strain studied permanently protected from injurious light rays.

In a series of 50 isolations, comparing the red tube method with the one ordinarily used, the number of cultures isolated were the same. In a few instances the colonies which developed in the light-protected tubes were larger than those growing in the uncolored tubes. This finding, though occurring accidentally at times, seemed to be fairly consistently within the range of error of observation in these experiments and suggestive enough to warrant further work on the subject.

SUMMARY

1. It seems desirable, in experimental work with tubercle bacilli, to eliminate the possibility of accidental attenuation of the bacilli by exposure to light.

2. Tubercle bacilli may be protected from injurious light rays if grown in red coated tubes, a precaution which is especially to be recommended in higher altitudes.

3. By the use of red glassware for the collection of infected materials, during the treatment of the materials and the cultivation of the bacilli, strains of tubercle bacilli may be isolated and preserved without suffering any appreciable change due to the photochemical action of light.

4. It remains for further studies to determine the importance of this method in maintaining the integrity of the bacilli.

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THORACIC RESTRICTION A MOST IMPORTANT ADJUVANT IN THE REST TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

SAMUEL GOLDEN

Anglum, Missouri

Since the institution of rest, rest in all its phases, in the treatment of tuberculosis, one has but to scan the literature to learn the remarkable and almost unimaginable results obtained from it. It is not my intention to criticise any other form of treatment, but to emphasize anew and evaluate the rest treatment.

Krause (1) in his address on "The Tuberculosis Problem" says, "Beware of the man who can perceive only one method of infection, one cause of onset, one diagnostic sign, one infallible test of prognosis, one method of prevention, one factor of resistance, one means of cure of tuberculosis." However, since specific therapy is not the most effective of the present methods of treating tuberculosis, one has to adhere to the method giving, everything taken into consideration, the best results, and that method is *rest*, complete rest, both of body and mind. It is relaxation and freedom from labor, from care, from nervous distraction and from boredom.

PHYSIOLOGICAL EFFECTS OF REST

We are all familiar with the increased metabolic rate and heart rate in tuberculosis, as in all infections, with a consequent increase in the elimination of products of infection, which tend to irritate the organs of elimination, particularly the lungs.

Exercise likewise increases the metabolic rate, rest decreases it, in health and disease. Therefore, it follows that rest slows the heart, lessens respiratory rate with a comparative decrease in local irritability and diminishes metabolism. In view of the fact that these changes do occur, it is then much easier to keep an individual in nitrogen balance

[1] Read before the Trudeau Society of St. Louis, April 5, 1923.

[2] From the Jewish Sanatorium of St. Louis, Missouri.

during rest than during exercise. When a person is at rest, as a result of decreased activity, there is a consequent diminution of tissue waste and the amount of food essential for tissue repair is necessarily decreased; therefore, the quantity of food ingested during rest being equal or nearly equal to the amount during exercise, it follows that there is a balance available for increased tissue building or reserve.

Mental and bodily rest puts the body in the best physical condition for resisting disease as well as combating already existing disease. If the utilization of energy, besides that needed for vegetative functions, can be directed toward fighting a disease, conditions that can be relatively brought about by rest, it becomes easy to understand how rest must be the *sine qua non* of treatment in any disease, and particularly in tuberculosis. *Rest is Nature's splint.*

Joseph H. Pratt (2) asserts that bed-rest out of doors yields a larger percentage of recoveries in a shorter period of time than any other method of treatment known. He quotes Rubel who, after immobilizing a lung in rabbits, infected the animals intravenously. The tuberculous process was more benign and more chronic in the lung kept at comparative rest than in the freely moving lung.

I fully agree with Pratt's statements. Where the difficulty lies, however, is in the carrying out of the method, even in sanatoria. Its applicability is not free from obstacles. The usual limited sanatorium nursing facilities constitute a great hindrance. Many sanatoria almost entirely disregard some evidences of activity of the disease as a determining factor during a patient's sanatorium stay, and permit patients to be up as long as the temperature approximates a whole degree of the normal mark.

At the Jewish Sanatorium of St. Louis patients are kept at strict bed-rest until all evidence of moisture in the lungs disappears. The results are remarkable and astounding, not only as evidenced by the clinical record but by the decrease in activity as well.

LOCAL REST

Since the need of keeping the lungs at rest, in order to promote healing, is the basis of the rest treatment in pulmonary tuberculosis, lung immobilization or restricted thoracic movement is not only profitable but essential, by whatever method may be instituted to give the best results with the least harm and discomfort to the patient. Since a

thorough conception of the mechanism of respiration in health is essential to the intelligent use of such methods, we may review our knowledge of the movements of the thorax.

In the 18th edition of *Gray's Anatomy* we read:

> During quiet inspiration the first and second pairs of ribs are fixed by the scaleni, and by the resistance of the cervical structures the last pair, and through it the eleventh pair, are fixed by the quadratus lumborum muscles. The other ribs are elevated so that the first two interspaces are diminished while the other spaces are increased in width. There is an elevation of the 3rd, 4th, 5th, and 6th ribs due to a slight gliding motion in the articular surfaces, leading to an increase in the anteroposterior and transverse diameters of the thorax: the vertical diameter is increased by the descent of the diaphragmatic dome, so that the lungs are expanded in all directions except backward and upward. Expiration is effected by the elastic recoil of the abdominal walls and by the action of the abdominal muscles which push back the viscera displaced downward by the diaphragm. During forced respiration all the movements during quiet respiration are here carried out, but to a greater extent, and the trapezius, serratus magnus, pectoralis and latissimus dorsi are called into play.

During forced respiration muscles that also assist indirectly are the sternomastoids, the deeper muscles of the back, such as the serrati postici superiores, and the erectors spinae.

Hoover, who has exhaustively studied costal movement says (3)

> Long ago observation was made that the infraclavicular region exhibited an undulatory movement during inspiration. This undulatory movement is due to the varying size of the first five ribs. The lengths of the upper five ribs increase from the first to the fifth. During inspiration the first rib is not elevated, but the second, third, fourth, and fifth ribs are elevated by the so called bucket-handle movement. The maximum movement of a rib will be in that portion farthest from the axis of rotation; consequently the external portion of the rib will move through a greater distance than the parts nearer the axis of rotation. The distance through which a rib will move in response to an inspiratory activation of the intercostal muscles will be limited by the extensibility of the underlying lung. The movements of the upper five ribs faithfully mirror the movement of the underlying lung . . . . Costal movements accurately mirror the movements of the underlying lung. When the respiratory excursions of the thorax are studied in this manner, the lungs and its bounding walls take on a new significance. The lung will be appreciated as a very lively organ which has a motility quite different from

the popular conception of an elastic bag which is alternately expanded and contracted *en masse* in obedience to changes in barometric pressure within the pleural cavity.

In a personal communication Hoover writes further

The lung is enlarged by the enlargement of the thoracic cavity in its circumference and in its length. The circumferential enlargement is accomplished entirely by the scaleni and the intercostals and the longitudinal diameter is enlarged entirely by the function of the diaphragm. I think you could limit the movement of the upper lung by strapping the upper thorax, and of course you can diminish the excursions of the ribs on one side by the use of adhesive straps on the skin. Inasmuch as the respiratory enlargement of the upper lung depends upon costal excursions, there is no doubt that you can limit the movements of the lung in that position. The fixation of the lung supposedly obtained by imposing an artificial pneumothorax is very misleading, for there is considerable movement in the lung that is collapsed in a pneumothorax. It is, of course, not so great and there is not the same degree of extension, but nevertheless a very considerable excursion. The fixation is not so complete as men fancy it is.

Various methods of lung immobilization are now employed, among them posture, controlled and diaphragmatic respiration, artificial pneumothorax, belts of muslin and other material around the thorax, strapping the chest with adhesive tape, plaster of Paris belts around the upper chest, the application of sand bags, etc. Of all these induced pneumothorax is the method commonly resorted to, in spite of its complications, sequellae, uncertainty of results and risk.

Artificial pneumothorax can be used only in a limited number of cases; in the early unilateral cases one hesitates because of the strong possibilities of cure by general rest with simpler measures. In moderately and far advanced cases, the procedure is rather difficult and at times impossible because of adhesions. At our institution it has been in use for the past eight years, that is, in certain cases only; but its intensive routine use was begun about four years ago. From our experience we would say that it has undoubted value in an extremely limited number of cases, but is to be decried as a routine method of treatment. We feel that, all things considered, it has accomplished nothing that would not have been equally well done by the application of external pressure with absolutely no risk. It must be remembered that by far the large majority of patients entering the Jewish Sanatorium are in the moderately advanced and far advanced stages of the disease.

Webb (4) and his associates investigated the value of simple posture in the treatment of pulmonary tuberculosis. They found that patients who rested most of the day and night on the affected side improved much more rapidly and, altogether, did better than those treated otherwise. By their method the weight of the body tends to restrict thoracic movement and in this way promote local pulmonary rest. Knopf (5) states that by his method of breathing many patients from the very beginning of treatment can reduce the number of their respirations to eight, seven and even fewer per minute, and thus comparatively rest their lungs. In September, 1921, Sewall and Swezey (6) reported cases treated with external thoracic compression by encircling the upper part of the chest with belts made of dressmakers' belting. Their results were gratifying, inasmuch as these included general improvement in the temperature range and a marked lessening of symptoms of toxemia. Beasley (7) also advocates a belt applied to the lower part of the chest, because he believes that the lower chest expands more and its respiratory excursions may therefore be limited more easily.

Nathan Levitt (8) reports very favorable results from the use of a plaster cast around the thorax from the second to the fifth ribs.

Immobilization of the thorax with adhesive tape in the treatment of pulmonary tuberculosis was done by Denison (9), as long ago as 1898 with very gratifying results. He believed unilateral thoracic restriction by means of adhesive tape to be most serviceable in checking pulmonary hemorrhage, and contracting and limiting cavities.

In our institution unilateral restriction by means of adhesive tape, applied to the affected side, was begun, as a routine procedure, about six years ago. It is done on all patients who, after six weeks of absolute bed-rest, fail to show improvement, and especially on those in whom there is reason to believe that the process is progressive and more extensive on one side. It is always applied in unilateral conditions, and in bilateral conditions on the more involved side when it appears that the unstrapped side would take care of a patient's respiratory requirements. It is resorted to in all cases of pulmonary hemorrhage in which induced pneumothorax is difficult or rendered impossible by complications such as adhesions, etc.

Results: In general, results may be said to be most gratifying. It is the rule for patients to request the reapplication of external compression, when for some reason it has been discontinued. There seems to be no doubt that improvement follows thoracic restriction if by improvement

we understand a diminution of cough and daily output of sputum, a lowering of temperature and a general increase in the comfort and satisfaction of the patient. We likewise have X-ray evidence, before and after unilateral strapping of from six to eighteen months, in which we believe we can demonstrate unmistakable evidences of scarring with limitation and contracting of the tuberculous process. In addition, we believe that the uninvolved portion of the strapped side shows a distinct tendency to a hyperplasia. Even admitting that the restriction of lung movement, by external pressure, accomplishes but little good, the mere fact of a physical procedure reminds and encourages the patient to fight the harder.

Our experience has firmly convinced us that, all things considered, nothing is so valuable in the treatment of pulmonary tuberculosis as pulmonary rest in addition to bodily rest. The easiest, safest and as efficient as any other method is the application of pressure to that half of the chest overlying the diseased lung.

The method we employ for strapping the chest with adhesive is as follows:

From seven to nine strips of adhesive are cut. These vary in number according to the vertical diameter of the chest. Each strip is 2 inches wide, and long enough to encircle the chest on the affected side during extreme expiration, from a point an inch beyond the vertebral border, starting in the upper chest but not too high to pinch the axillary folds, on the unaffected side, to a point 2 inches beyond the parasternal line of the unaffected side. The skin on the side upon which the adhesive is to be placed is now shaved, if necessary, sponged and rubbed with 95 per cent alcohol. The armpit is now protected from the irritating effects of the adhesive by a piece of gauze large enough to cover the entire axilla. The patient is placed in a semirecumbent posture and all pillows removed, the patient resting on the unaffected side and the operator facing the patient. The arm on the side to be strapped is abducted and flexed, so that the palm touches the head. A strip of adhesive of the desired length is now anchored and held by an assistant in the anchorage points previously described, that is, starting immediately below the axilla, an inch beyond the vertebral border of the unaffected side. The patient is now instructed to inspire and expire forcibly, and to hold his breath when the maximum of expiration is reached. He is to instantaneously, but slowly, turn his body away from the operator, so as to more or less approximate the supine position. While the patient is thus turning during extreme expiration, the operator makes traction, applying as much pressure against the chest, while encircling it in a horizontal plane, as the strip of adhesive will permit without

tearing. In this way the pressure and traction brought to bear by the operator are supplemented by the pressure of the weight of the patient's body during its rotation. It is a common thing during the procedure for several strips of the best adhesive to be torn, purely by the force applied. The second strip is placed below the one just described and overlaps it by an inch. The same manoeuvre is gone through for each succeeding strip, until a point a half-inch below the external costal margin of the tenth rib is reached.

A large enough pad, when compact and placed in the supraclavicular fossa of the affected side and held in place by a strip of adhesive, will supposedly limit expansion in that region. This pad is held in place by another strip of adhesive drawn tightly across the shoulders from anywhere in the interscapular space to the sternocostal margin. This we call an apical strap.

So firmly are we convinced and so enthusiastic is our staff in the belief that thoracic restriction is the most important aid in the rest treatment of pulmonary tuberculosis that a St. Louis firm became interested in devising a splint for external thoracic compression which led to the development of an inflatable jacket or pneumatic chest splint. A description of this splint is as follows:

A half-vest, encircling one-half of the chest, so that the front border is in midsternal line and the back border in midspinal line, is made so as to fit snugly the contour of one-half of the chest. The outer covering of this jacket is made of a nonstretchable material, commonly spoken of as "reindeer cloth," which is employed in the manufacture of women's white shoes. The lining, which is in proximity with the skin, is made of a high-grade sateen. Between the outer and inner coverings is the inflatable part, which is a rubber bag, also cut to fit the conformation of half the chest as desired. This bag is vulcanized, so that it is absolutely air-tight, and is tested against leakage on pressure. It is perforated at different places with apertures measuring one-half inch in diameter, for the purpose of skin ventilation. The outer covering is likewise made of numerous eyelets for the same purpose. It is connected with the outside air by means of a rubber tube with an air-tight valve, slipped through an opening in the outer covering to become imbedded in a pocketed groove, the cover of which is fastened with several clasps. The outer covering and rubber bag are cemented together so that traction on the cloth, or outer covering, causes at the same time traction on the rubber bag. Along either side of this jacket, and continuous with all its coverings or layers, are three straps, made of the same material as the outer covering, which buckle in front and hold it fast. The jacket is inflated by means of an ordinary atomizer bulb.

The advantages of this appliance are ease of application and removal, variation in pressure in accordance with individual needs, constancy of pressure, once inflation is established, and low cost compared with a prolonged course of adhesive strapping.

The jacket is to be worn from six to eighteen months. For comfort, patients may deflate it on retiring at night. Constriction by the jacket without inflation has been noted to restrict a certain amount of thoracic movement. The use of the appliance in our institution is of comparatively short duration and any attempt at determining its value is premature, although its preliminary use is distinctly encouraging.

CONCLUSIONS

1. Bed-rest, coupled with thoracic restriction, or pulmonary rest, brought about by external pressure through whatever means, gives the best results, with the least risk or discomfort to the patient and is unsurpassed in the treatment of pulmonary tuberculosis.

2. External thoracic compression immobilizes lung extensibility, and thereby hastens healing.

3. By the method toxemia is diminished.

4. By the proper application of external thoracic compression pulmonary hemorrhage may be checked.

5. Pain, especially of pulmonic or pleural origin, is instantly relieved by the proper use of the method.

6. The ease of application and freedom from risks and complications make the method especially serviceable and most profitable, both to physician and patient.

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THE TEACHING OF TUBERCULOSIS IN MEDICAL SCHOOLS

WM. CHARLES WHITE

There has grown up in the past years, and there still is, a dissociation between the medical profession and the active agents of the tuberculosis movement. There is also a certain lack of mutual respect between the two groups. I think the origin of the existing condition is the group of physicians who have been responsible for the medical work of tuberculosis, as specialists in this field. They have not only continuously pointed out the ignorance of the profession to the lay workers but they have grown to believe the truth of their statements. I am afraid they do not realize how frequently this calumny has been reiterated in their discussions and writings, and yet I am sure the ignorance of the general profession is not greater on tuberculosis than on other subjects of medicine. The physician who has devoted his time to tuberculosis has not gained his knowledge from his medical school, as a rule, nor is he often skilled in other fields of medical practice. This situation is the more to be deplored in that the most important factor in the whole tuberculosis movement is the practising physician. Tuberculosis is an infectious malady, coming under his care not only in its diagnosis but also in its treatment and in its suppression. This fact has been, perhaps, the most significant outcome of the Framingham experiment, in which those in charge have repeatedly stated that the most powerful factor in the success of the work there was the consultant physician, Doctor Bartlett, who devoted his time to the instruction of the doctors of that community.

I have tried, in the preparation of this paper, to seek out the faults in our present situation and to suggest certain remedies, that our work may be uniformly more efficient. In obtaining the data upon which to base the suggestions, I have consulted the deans of the class A medical schools, many practitioners of medicine in different parts of the country, and many of my friends who devote themselves more especially to tuberculosis and the literature on the subject.

The groups concerned in a solution of the problem are the medical schools with their teaching staffs, all practising physicians, the national, state and municipal tuberculosis associations, the specialists in tuberculosis and certain institutions undertaking graduate instruction.

The response from the medical schools is what one who is conversant with modern education would expect. Knowledge has grown to such an enormous mass that our whole educational system is in a turmoil, both as to method of instruction and as to what should be taught. So great is the turmoil that we would seem to be devoting our educational institutions to athletics and various other specialities, until the matter is solved; throwing out the fundamentals, one after another, as the mound dwellers did the refuse which built their kitchen middies.

The situation in the medical schools is that common to all educational institutions, a time of reconstruction in method of teaching, an attempt to determine what constitutes the essential substance to be taught and a struggle against the time demanded by the specialists. The irritation against the demands of the special fields of medicine for time on the curriculum and more recognition was, perhaps, the most dominant note in the answers received from the deans of the medical schools. I have much sympathy with them. Some of the answers suggested constructive changes which will be referred to later. The great difficulty is probably in the enormous growth of knowledge and the inability of teachers to choose what is essential in the substance to be taught during the years allowed for medical education. We have probably fifty years of undigested knowledge on our shelves, in journals, magazines and monographs. Not one of the answers expressed satisfaction with the way in which tuberculosis is taught to-day.

Among the practising physicians, the lack of interest in tuberculosis is explained by their feeling of inability to handle tuberculosis at home, the absence of any specific form of treatment for the disease, the loss of their patients, through sanatoria, specialists in tuberculosis and climate, and the distrust of them which has largely resulted from the methods of the various tuberculosis societies educating the public. The growth of the numbers of irregular practitioners to whom the chronically ill go, the publicity which the press gives to all vaunted cures, have moreover, an influence on the attitude of physicians to a problem which is kept so constantly before the public. They feel that there is a great failure in medical schools which do not teach them how to meet the condition which they meet in practice and in the national association which does not give to the public authoritative knowledge through the lay educators in this field. I have the greatest sympathy with the physicians.

Never, in the history of the world, has there been so large and powerful and wealthy a voluntary organization dealing with a public health problem as the National Tuberculosis Association, with its constituent state and municipal units. It expends annually well over $5,000,000, and this is in addition to the four or five hundred million which it has been largely instrumental in persuading the various federal, state, county and municipal governments to spend annually, and in addition to the enormous sums spent by private individuals for the care of their sick, and in addition to the loss of other earnings by the tuberculous sick and those who nurse them. That this enormous expenditure, by present methods, does not produce permanent results, the war has brought out in a significant way. While we have burned an enormous amount of infected sputum, we are not yet sure that tuberculosis can be controlled in this way, nor have we found the methods of relieving suffering with a sure hand. The faults with these organizations are mainly in the uncertainty of knowledge which they use. The uncertainty is in no way more evident than in the change in the substance of the education, from period to period; sanatoria, hospitals for advanced cases, dispensaries, eggs and milk, fresh air, have all been emphasized from time to time; none separately, or all together, are either adequate or possibly essential, if every practising physician were taught and practised the fundamentals of examination, destruction of sputum, rest and continuous supervision.

Let us take the concrete example of our terminology—*Early, Moderately Advanced, Far Advanced,* and *Cured, Apparently Cured, Improved.* These are the indefinite, unscientific terms we use, the best we have been able to devise. They invade our literature and lead to the uncertainty of the doctor and the advice and promise which he can give to the sick. Again the physician is urged to get the cases early. No one dealing with tuberculosis can escape the fallacy inherent in this advice, as evidenced by the so called early cases that go on to death under the best of conditions and the more advanced cases that recover without knowing that they have been sick. Possibly the vast majority of cases are of a definite degree of secondary involvement, following their primary lymph node infection, when they first seek the physician's advice and he, very, very often, could not have got them earlier if he had examined them every six months. A study of the tuberculin testing and slaughtering of herds of cattle will bear some study and application in understanding the insidious, difficult problem in man. In this cattle

work, new cases, even extensive in involvement, arise continuously, in each six-months' interval between the tuberculin tests, in spite of the removal of all reactors following each test. How much more likely are we to have new cases of varying degree of involvement in the human family, with open cases constantly among them. Much of our present knowledge is in this shape; and still the voices of the educators, nurses, and social workers of the various associations never falter in the sureness of their utterances and promises that control is possible to us. Of all the vast resources of power and money of these associations, so little, so very little, has been spent to make knowledge surer or to help the essential physician to use such sure knowledge as we have.

Almost anyone will do to educate the public on tuberculosis in common with many of our other complex medical problems. A few weeks ago, I was approached, on the train, by the chief tuberculosis educator of one of the largest state societies and regaled, for two hours, with the value of Christian Science, which had cured her. She was daily before audiences, carrying our message. No wonder there is some failure in winning the respect of the medical profession, and yet it is on such knowledge as her simple mind and glib tongue could transmit that we base much of our work in a field that has baffled the best scientific minds of the past century. A nursing instructor, who holds a prominent position, asked me recently to tell her, in a few words, about vitamines, so that she could tell her nurses at her next class. I hesitated in my answer, thinking of the complex, unknown nature of this public bagatelle: while I hesitated, a social worker answered for me and I slipped away. Perhaps, a few words describes all we really know.

Of the specialists in tuberculosis, I hesitate to speak. Like Bernard Shaw, I feel their bread and butter is in the matter and their faults are largely from this reason. They are human. Many of them are winged with tuberculosis and isolated from the real problem of tuberculous life, which is a family and industrial one, and deal with an uninteresting slow sickness in sanatorium groups. Their natural cry against the general practitioner would not happen so often if every patient were well-to-do. They are, however, a great service to modern humanity, and alleviate and cure much of the suffering of the disease with which they deal.

The institutions of graduate instruction belong, in discussion, rather to the attempts at correction of our present dissociation, but, as I look over their curricula, they are devoted rather to making specialists, with a

complex course of instruction, than to a struggle to teach the essentials of control and care of the sick.

Reverting again to the medical schools, from which come our doctors; with whom, I believe, rests the great burden of the tuberculosis problem: what has been done by them to aid in the difficulty? The lack of time, in the face of growing knowledge, is their great shortcoming. To overcome this, they are pushing clinical teaching over into the post-graduate school and hospital year. These do not help tuberculosis so much, as the hospitals have been slow in making provision for even teaching facilities for this disease, even though its danger to others is almost at a minimum. The National Tuberculosis Association could do much more to create public opinion to help administrators to overcome the fear which keeps tuberculosis out of our general and teaching hospitals. Could medical schools do more? I feel that there is little doubt that they could by condensing the time now taken for tuberculosis by almost every specialist and using the time saved in correlation clinics, where the specialists take part, under the member of the Chair of Medicine dealing with tuberculosis, along with the pathologist, the anatomist, the chemist, the physiologist. At these correlation clinics, tuberculosis of various parts of the body should be presented and the general and special treatment outlined, so that the student would gain some notion of the disease, as an entity and the essentials of its care. To-day, tuberculosis is too often presented only as pulmonary tuberculosis and each specialist deals with tuberculosis elsewhere in the body, as he chooses, as if it were not the same tubercle bacillus which causes it. In the second place, some part of the time might be saved that is now devoted to trying to make expert auscultators and percussors out of men who can never be such, any more than all, who strum the piano, can be musicians. Many lack the acuteness of hearing and touch. The time saved could be devoted to teaching students the essentials which all can use, frequent examinations of sputum by state, municipal and private laboratories, the use of a four-hour temperature record, the measurement of twenty-four hours' sputum, as an index of involvement and improvement, the destruction of sputum, the protection of the mouth in coughing, the arrangements of a house for domiciliary care, the use of rest in diagnosis, treatment and prognosis. These are, in part, the special knowledge of the experts: anyone can use them and they are lacking in the practitioners' daily practice. Teach the medical student, in the school, the things he can use daily with

good results and his interest will grow. I believe, further, that every dean will gladly welcome helpful suggestions, just as he now resents criticism and demand for more time, made often with little knowledge or sympathy with his overwhelming difficulties.

Now, in what can the national and state associations aid to correct the difficulties and secure the essential help of the profession?

First, by using part of their funds to provide carefully planned instruction for the state secretaries and those intrusted with the education of the public, so that this may be accurate and as uniform as possible and changed from year to year, as knowledge grows.

Second, for the national and state associations, in conjunction, to employ a consultant in medical education and curricula, to aid the medical schools in saving time and utilizing the time to the best advantage, in giving to medical students the most practical knowledge, in alleviating the suffering from and suppressing the disease. Many schools would welcome such assistance and it would soon become universal. This should be done in consultation with the council of the American Medical Association on medical education.

Third, for state associations to provide consultant physicians for communities, for work similar to that done by Dr. Bartlett in Framingham. Through these consultants, uniform practice could be gained and special students chosen for the postgraduate schools.

Fourth, the national and state associations should devote more and more funds to the work of medical research: to put in the hands of physicians and executive officers, annually, more accurate data.

I feel that the answer will be made that the budget is already overloaded, but what I suggest is not more money but another and, I feel, a better use of the money. As the federal, state and municipal governments take up the hospital, dispensary and educational work, there is less need for voluntary organizations to act in these fields, and they should release their expenditure, in this way, as soon as it is practicable and devote the time and funds to the search for more sure and permanent ways of securing our purpose, the cure and suppression of tuberculosis.

TEACHING NORMAL CHEST FINDINGS TO MEDICAL STUDENTS[1]

J. A. MYERS

Minneapolis

In looking over the medical school curricula of the United States there appeared, in most schools, a wide gap between the laboratory and the clinical subjects. Students were taught the anatomy, physiology and pathology of the chest, but little time was devoted to teaching the findings in the living normal chest. The result was that students with such training were passing into the clinical years, in which instructors were trying to teach the physical signs of disease. The students were asked to examine diseased chests with no knowledge of how to distinguish between normal and diseased areas. The result was that at the end of the brief time allotted to this particular kind of work they found themselves without an adequate conception of the normal, to be used as a point of departure when studying the abnormal chest.

In the autumn of 1920, Dr. S. Marx White, Chief of the Department of Medicine, Medical School, University of Minnesota, asked that a course be organized for teaching the findings in the normal chest. In talking with many of the junior and senior medical students and a number of recent graduates of the University of Minnesota, and other medical schools, there was a general expression from them that they rarely felt sure of their chest findings, particularly of the lungs. Under these circumstances there appeared a real need for a course, in addition to the course in general physical diagnosis, covering the findings in the normal living chest to bridge the gap between the laboratory and clinical subjects. Steps were taken to organize such a course in the University of Minnesota. This work was greatly stimulated, however, by a symposium on education in tuberculosis at the seventeenth annual meeting of the National Tuberculosis Association. Dr. Walter C. Klotz presented a splendid paper on "Undergraduate Instruction in Tuberculosis in the University of Virginia;" but, when asked by Dr. Moorman,

[1] From the Department of Internal Medicine, University of Minnesota.

"Where does the study of the normal body come, in the sophomore or junior year, and how much time is given to that?" Dr. Klotz replied that "the normal physical diagnosis is supposed to have been taken up before the end of the second year, and students are supposed to come prepared with this knowledge of physical diagnosis, but I want to be frank and say that they do not."

Dr. Kennon Dunham, in discussing papers read by Drs. E. R. Baldwin and A. K. Krause, spoke as follows:

> If the student is once thoroughly grounded in knowing the normal chest, in knowing where normal bone is, where normal loss of resonance can be found, how the breath sounds change over the chest, and that marginal râles are heard in the tuberculous chest, and if he comes to know what those sounds mean, what inspiration or expiration is, then he is interested to know what is inside of that. Then is the time to open your X-ray picture up to him. Do not stop there. That leads him to what? To a knowledge that he wants to get, to the "pathology." He wants to get over then to the postmortem school. Those students, after all, are most vitally interested to find out, as a result of autopsy, whether their diagnosis was correct or not. You have then accomplished the first thing in order to get this education to the student, that is, you have aroused the students' interest.

Col. George E. Bushnell stated that

> the way to learn physical diagnosis practically, I take it, is to study the normal chest, and I am glad that Dr. Dunham said what he did about that because there is a wealth of material going to waste. A man who can tell you, accurately, everything there is in the normal chest in the way of variation of breath sounds, in the way of percussion sounds, knows diagnosis enough so that he can go on by himself. As far as the acquirement of technique is concerned, you acquire technique only by actual practice. If you have to examine a man who is sick, you have to spare him; you should spare him. However, you either hurt the patient or you do not get enough practice. On the other hand, you can take the healthiest man that ever lived and work a number of days on his chest and there is no doubt that you can learn something every day that is worth while.

I am now thoroughly convinced that it is just as logical and necessary to teach the physical findings in the living normal chest before the student undertakes clinical work, as it is to teach anatomy before he attempts pathology.

This course in normal chest was first offered at the University of Minnesota during the fall quarter of 1921–1922. It was repeated, and the time was increased during the winter and spring quarters of the same year. The time now given to it consists of three actual hours per week of class and demonstration work, and the students spend considerable time outside of class hours examining normal chests.

The work consists of a brief review of the anatomy and physiology of the chest, physical examination (inspection, palpation, percussion and auscultation), functional tests, X-ray findings in the living normal chest, and examination of the chests of obese and senile individuals and children.

Anatomy: It has been stated that he makes fewest mistakes who knows his anatomy best. Owing to the fact that anatomy is so easily forgotten, a few periods are devoted to a review of the more important points in the anatomy of the chest. Time does not permit the student to make any dissections, but preparations of special dissections, frozen sections, etc., are brought into the class room, where the important points from the standpoint of disease of the chest are demonstrated and discussed. One period is given to the lymphatic system, and another to the nervous system, so far as they apply to the chest. The practical consideration of the development of the chest from the embyronic stage to adult life is given in one or two periods.

The surface of the living chest is next studied. The bony landmarks, muscle masses, etc., are demonstrated, and the more important internal organs are mapped out on the surface.

Physiology: The physiology of respiration and circulation are reviewed. A considerable time is devoted to the study of intrapulmonary and intrathoracic pressures. When possible, the students are taken to one of the hospitals and given an opportunity to see the manometer readings while a patient is receiving artificial pneumothorax treatment.

Physical Examination: For this phase of the work the students act as subjects and examiners, or a number of ambulatory patients with negative chests volunteer to act as subjects. The subject removes all clothing to the waist and the various points in inspection, palpation, percussion and auscultation are demonstrated: for example, the phrenic wave, cardiac impulse, variations in tactile fremitus and tissue resistance over the chest, different percussion notes, unimportant sounds, such as muscle and skin friction sounds, the various breath sounds, the transmission of whispered and spoken voice over different parts of the chest,

heart sounds, rhythm, etc. When all important points have been demonstrated, the students are required to make complete physical examinations on several normal chests. In short, an attempt is made to familiarize the student, not only with the method of examining the chest, but also with the actual physical findings of the normal chest.

Weight and Vital Capacity: The students are taught the various methods of ascertaining the theoretical normal weights of individuals. A short time is also spent in teaching the significance of the vital lung capacity test and the methods of arriving at the percentage of the normal which any given individual possesses.

X-ray Examination: After the students have gone over the physical findings of the normal chest several times, they are taken into the X-ray room. Here normal subjects are fluoroscoped; and considerable time is given to the positions, size and outline of the heart and aorta, as well as the contour and excursion of the diaphragm. The extent of the lungs and the hilum shadows is observed. One of the subjects is asked to take the duodenal tube. This gives the student an opportunity to follow the metallic part of the tube through the esophagus and into the stomach. A small air-pump is then attached to the free end of the duodenal tube and air is pumped into the stomach. The students see the gas bubble enlarge and, finally, an encroachment upon the diaphragm and heart is observed. This is a good time to emphasize the close relationship existing between the stomach and heart, and call attention to the symptoms which may accompany overdistention of the stomach. Plates of normal chests are placed in the stereoscope and the students are given sufficient time to make a careful study of them. An attempt is made to point out the advantages of stereoscopic plates over fluoroscopy and single plates in studying the details of the lungs.

When the X-ray examination is completed, the students examine the chests of several senile individuals. Special attention is called to the conformity of the chest, emphysematous type of breathing and marginal râles. Much interest is added to the work when the students are told that similar râles exist in certain diseases of the lungs.

A few adult obese individuals are examined to emphasize the difficulties encountered in the examinations of such persons.

The students are given an opportunity to examine the chests of several children. The important differences between the findings in the chest of the child and the adult are pointed out at this time.

A written quiz is given every week. Questions may be asked on any or all phases of the work given prior to the time of each quiz. Such quizzes stimulate frequent reviews of the entire subject matter. At the end of the course each student is assigned a patient with very definite pulmonary disease. The student is requested to apply every phase of the examination, including the study of stereoscopic plates, to this patient, and report any deviation from the normal that he has been able to detect. This constitutes the final examination.

This work is being offered as an elective course. The first quarter it was offered 6 students elected it, the second quarter 21, the third 22, and the fourth 30 students. Therefore, 79 students have elected this course during the four quarters it has been offered.

The course is designed for students who are ready to begin clinical courses. It has been made prerequisite to an elective course in diagnosis and treatment of diseases of the lungs. Students electing this latter course meet in one of the sanatoria for the tuberculous, where they examine and study patients in all stages of disease.

The results of this work have been very gratifying. Students who have taken the course in normal chest work enter into the work in diseases and treatment of the lungs with much enthusiasm and an excellent understanding of the normal which gives them confidence. From the beginning they have very little difficulty in detecting the diseased areas. At first they do not know how to interpret the abnormal findings elicited, but they do know that such findings do not exist in the normal lungs. As time goes on, they are taught differential diagnosis which they grasp very readily. Recently an opportunity presented itself to make a comparison of the work of these students with that of a group who had taken no special training in normal chest findings. This comparison, together with other observations, proved that students with such training accomplish fully twice as much in a given period of time as those without such training.

This experience has convinced me that a well-organized course in normal chest findings, in addition to the general course in physical diagnosis, has a place in every medical school. It will make the students more confident, enthusiastic, and desirous of learning to detect disease, and in the end will be productive of diagnosticians capable of detecting diseases of the chest in their early stages.

A TUBERCULOSIS LIBRARY AND ITS CLASSIFICATION

A NEW ADVENTURE IN THE LIBRARY FIELD

ADELINE M. MACRUM[1]

Pittsburgh

The library of the Tuberculosis League of Pittsburgh was organized to fill a very real want of the community, and is somewhat of a pioneer in its field. Aside from the library of the National Health Council, which it antedates, I believe it is the only health library with a country-wide circulation, open to all comers. As to local facilities, Pittsburgh has a number of medical libraries; most of them are restricted to a certain group, and none are circulating libraries open freely to the public. Furthermore, the other libraries are general in scope, and have a very limited interest in tuberculosis, so that the material they contain on this topic is scant.

From its inception in 1906, the founders of the Tuberculosis League had in mind the building up of a library on tuberculosis. Periodicals were bought, together with a few of the classics, and this small nucleus was added to from year to year. The scope of the library was gradually broadened to include a number of allied subjects, such as physiological chemistry, bacteriology, all respiratory diseases, public health nursing and, in fact, the whole field of public hygiene.

Early in 1921 the collection was catalogued, and the library, while previously functioning to a limited extent, now opened its doors to all residents of Allegheny County. Our readers include school teachers, ministers, doctors, medical students, nurses, lawyers, librarians, social workers, club women, and all interested in the public health. Our service to the public is entirely gratis, and comprises the use of our reading room; the preparation of bibliographies; the answering of

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reference questions by telephone, letter or in person; advice as to the best health books to purchase; the circulation of health literature, and the giving of health talks.

At present we receive every month about eighty periodicals, the more important of which are later bound to form part of our permanent collection; each year we add fifty to a hundred of the best books published on hygiene and tuberculosis. By watching the articles which appear in the journals we procure from the authors reprints of all the more important papers for our large reprint collection; these are of value in connection with our teaching work in the University of Pittsburgh and elsewhere, as it is much easier to carry about three or four reprints than the same number of heavy, bound periodicals, and it keeps the latter on the shelves for reference use.

I have often been asked by physicians and librarians as to how our material is classified. For the benefit of these many inquirers, it may be of interest to relate my own experience and the scheme finally evolved.

When I took charge of the library of the Tuberculosis League of Pittsburgh there were quite a few text books, bound periodicals and pamphlets upon the shelves, but no attempt at arrangement. My first thought was to use the Dewey decimal system, as it was one with which I had worked for the previous eight years. I proceeded slowly and cautiously, as medicine was a new field to me; after a month of study and experiment, the fact impressed itself upon me that the Dewey system would not do for this collection, and a system originally designed for medicine alone would be much better.

The systems of the Library of the College of Physicians, Philadelphia, of the Surgeon General's Library, and of the Boston Medical Library were studied. Miss Isabel Towner of the National Tuberculosis Association was kind enough to furnish me with a copy of the "modified Dewey" in use there. I also had a copy of a scheme dealing with the respiratory diseases, translated from a proposed expansion of the Institut International de Bibliographie.

After a careful study of the above methods, I decided that the Boston Medical Library classification best suited my purpose, and began at

once to catalogue my collection. This choice was justified, for the system has worked out very well, and about a year later was adopted as the standard classification recommended by the Medical Library Association, a national organization. It is now in use in many medical libraries, large and small.

The Boston method was all very well for our general material, but the contents of the Tuberculosis League Library is highly specialized in tuberculosis, and it soon became manifest that some subdivision of the main headings, *12M Tuberculosis*, and *12N Pulmonary Tuberculosis*, would have to be made. The Medical Director objected to scattering the material, as for example, using *18F, Tuberculosis of the Bones, Joints, etc.*, under the section on the *Locomotor System*, or *24F*, under *Gynecology*. He contended that the disease is the same no matter in what part of the body it may be found, and for our purposes it should all be grouped under *12M* and *12N*.

The following amplification was accordingly made, and is published in the hope of being of assistance to other tuberculosis libraries. During the two and half years it has been in use, it has been quite satisfactory. It is far from perfect, however, and is merely submitted as a beginning. Any criticism and suggestions will be most gladly received:

12M—TUBERCULOSIS

12M—*General data:* annual reports, etc.
12M1—*Causes of infection:* environment, heredity, etc. considered here
12M2—*Diagnosis*
12M3—*Prognosis*

12Mb—*Tubercle Bacillus*
- 12Mb1—Varieties (Avian, Bovine, Human, etc.)
- 12Mb2—Biochemistry
- 12Mb3—Cultural characteristics
- 12Mb4—Extracts: tuberculins (various types)
- 12Mb5—Infection: virulence; reinfection, etc.
- 12Mb6—Morphology
- 12Mb7—Serum reactions: complement fixation; allergy, etc.

12Mb8—Staining properties
12Mb9—Reactions to certain agents, as light, heat, chemicals, bactericides
12Mb10—Tissue reactions: resistance, cellular immunity, etc.
12Mb11—Research problems (general discussions of research on the bacillus)
12Mb12—Metabolism
12Mb13—Portals of entry
12Mb14—
12Mb15—

12Mc—*Tuberculosis, Forms. Acute miliary*
12Md—*Tuberculosis, Forms. Occult*
12Me—*Tuberculosis of various parts of the body:* arranged alphabetically hereunder, except tuberculosis of the lungs, for which see 12N

12Mf—*Treatment*
12Mf1—(not used)
12Mf2—Sanatoria and hospitals
12Mf3—Treatment at home
12Mf4—Open air treatment
12Mf5—Occupational therapy
12Mf6—Tuberculins and vaccines; sera
12Mf7—Heliotherapy
12Mf8—Quartz light and ultraviolet ray
12Mf9—Climate
12Mf10—Drugs and chemotherapy
12Mf11—Surgery
12Mf12—Quack "cures"

12Mg—*Patient after arrest:* vocational rehabilitation; follow-up work; farm colonies

12Mh—*Sociological aspects of tuberculosis*
12Mh1—Tuberculosis and war: data on soldiers, including vocational rehabilitation of soldiers, and data on civilians under war conditions only
12Mh2—Educational publications: nontechnical material for lay readers

12Mh3—Educational and preventive work in general
12Mh4—Educational and preventive work of municipalities
12Mh5—Educational and preventive work of counties
12Mh6—Educational and preventive work of states
12Mh7—Educational and preventive work of nations
12Mh8—Educational and preventive work, international
12Mh9—Tuberculosis and occupations; dust hazard, etc.
12Mh10—Tuberculosis in certain races: Indians, Negroes, Jews, Italians, Irish, etc.

12Mi—*Tuberculosis in animals* (alphabetically arranged by animal)

12Mj—*Tuberculosis in children*

12N—PULMONARY TUBERCULOSIS

12N—*General data*

12Na—*Pulmonary tuberculosis with complications*
12Na1—with influenza
12Na2—with pregnancy
12Na3, etc.; subdivisions may be added to suit material

12Nb—*Diagnosis*

12Nc—*Prognosis*

12Nd—*Forms of Pulmonary Tuberculosis*
12Nd1—Acute pneumonic
12Nd2—Acute miliary
12Nd3—Chronic pulmonary
12Nd4—Fibrosis
12Nd5—Bronchopneumonic

12Nf—*Treatment* (Only methods of treatment peculiar to pulmonary tuberculosis are classified here; same subdivisions as 12Mf may be used)
12Nf11—Artificial pneumothorax

12Nh—*Sociological aspects:* mortality data, etc., peculiar to pulmonary tuberculosis

12Ni—*Tuberculosis of the lungs in animals*

12Nj—*Tuberculosis of the lungs in infants and children*

CHEMICAL EVIDENCE ON THE PHYLOGENETIC CLASSIFICATION OF THE TUBERCLE BACILLUS[1, 2]

THE PLANT OR ANIMAL QUESTION

ESMOND R. LONG

Chicago

Bacteria, largely on the basis of two properties, namely, spore formation and marked capability in the direction of chemosynthesis, both of them recognized characteristics of plant life, have been generally classified as members of the vegetable world. To be sure, the spores do not bear the same relation to reproduction in bacteria as in plants, but there is a superficial resemblance. Exceptions have been made with respect to certain "higher bacteria." The question of their classification has recently had some airing in *Science*. One investigator would limit plants to "those organisms possessing chlorophyl or descended from chlorophyl-possessing ancestors." Bacteria, with the exception of certain filamentous forms, are thus definitely excluded. Presumably this definition (1) does not mean that bacteria be shifted from the position they have usually held in general opinion, as forms of plant life to be classified forthwith among the animals. The division of Nature into Animal, Mineral and Vegetable Kingdoms may leave more sovereignties unspecified than

[1] From the Department of Pathology of the University of Chicago, and the Otho S. A Sprague Memorial Institute.

[2] The analysis attempted in this paper has developed out of studies on the chemistry of the tubercle bacillus, which for several years have been pursued under a grant from the National Tuberculosis Association. In 1921 the Association, on the recommendation of its Committee on Medical Research, appropriated a sum of money for the furtherance of investigations, then being conducted by the author, on the nutrition of the tubercle bacillus. In the course of these investigations it became highly desirable to obtain exact information on the nature of the nucleic acid present in the tubercle bacillus. The well known researches of Dr. Treat B. Johnson on nucleic acid chemistry led the author to ask him to study this phase of tubercle bacillus chemistry, and to devote part of the appropriation, assigned by the Association, to this work. The important researches on tuberculinic acid by Johnson and Brown, from the Sheffield Chemical Laboratory of Yale University, referred to in this paper, were made possible by this financial aid. They have been reported, in part, in the *Journal of Biological Chemistry*, December, 1922, and the AMERICAN REVIEW OF TUBERCULOSIS, June, 1923, and are being continued, and will be reported by them in detail later.

the Kingdom of Heaven, to which the puzzled child assigned the fairy tale prince. Fitting living beings into systems seldom leads to results objection-free. We have left far behind the day when one could say comfortably with Linnaeus that plants live and grow, while animals live, grow and feel.

Discovery makes for complexity more often than the reverse. Once a division of the universe into organic and inorganic matter was easy; until Friedrich Wöhler transformed ammonium isocyanate, a compound belonging to the world of nonliving things, by simple fusion and resultant intramolecular rearrangement, a procedure in which matter was neither gained nor lost, into the well-known derivative of life processes, urea. The Gordian knot tied thereby in the classification of chemistry was not solved until an official committee of chemists rudely severed it by arbitrarily ruling that all compounds containing the element carbon were *organic*, and all the rest *inorganic*. In these later days, however, when specific atoms have been divided into nonspecific electrons, and chemical elements are polymers of something common to all, a distinction based on the individuality of an "element," is in danger of not distant collapse.

Solution of the plant vs. animal controversy has been sought in some instances[3] in the establishment of a separate class, the protista, intermediate between plants and animals, or distinct from either. This may seem a logical escape from a vexed problem, and yet, in addition to its despairing aspect, serves to divert attention from interesting relationships of considerable evolutionary significance between living forms in question and one or the other of the two great groups. A very useful purpose is served by the effort to fit all living beings into one or the other class in so far as the evolutionary point of view is maintained, in that attention is kept focused on the root of all biological problems.

If Linnaeus's psychological distinction is unfit and the methods of morphological differentiation are inadequate, there remains yet another basis on which bacteria may be classified with respect to plant or animal tendencies. This is a chemical one. Wells (2), in his "Chemical Pathology," refers twice to the possibility of distinguishing bacteria as plants or animals on this basis. One means is the determination of the type of nucleic acid present, nucleic acids being divided at present into plant and animal types; the other is in the finding of such typical plant products as cellulose or hemicellulose, on the one hand, or the animal sub-

[3] Enough for the establishment of a journal, the *Archiv für Protistenkunde*.

stance *chitin*, familiar in the shells of crustaceans and wings of insects, on the other. Chitin is indeed not limited in its distribution to the animal kingdom, as many fungi of undoubted plant affiliations contain a certain amount of it (3) (4); but its content in certain animal tissues is striking. Additional chemical sources of differentiation are not wanting, even though an inquiry, comprehending all the fields within which a distinction may be made, must meet with but infrequent reward and leave many gaps, because of the sketchiness of our present knowledge of bacterial chemistry. Enough knowledge is at hand for a good start, however.

It so happens that the chemistry of the tubercle bacillus has been investigated more extensively than that of any other bacterium. If any microörganism is at present able to supply us with chemical information useful in the classification of bacteria, it is the tubercle bacillus. In the pages to follow the composition and metabolism of this bacillus will be examined with respect to this problem.

The following very abbreviated classification of the materials entering into the make-up of living things, and of the processes by which living things are made up, will serve as an outline for the consideration below of what is known concerning the tubercle bacillus which might apply in the problem under consideration.

Composition

Proteins	*Carbohydrates*	*Lipins*	*Water*
Simple	Monosaccharides	Alcohols	*Salts*
Conjugated	Polysaccharides	Fatty acids	
Nucleoprotein		Waxes	
Glycoprotein		Phosphatids	
Derivatives			
Amino acids			

Metabolism

Energy production	*Carbon metabolism*	*Nitrogen metabolism*
Oxidation	Absorption	Absorption
	Synthesis	Synthesis
	Excretion	Excretion

PROTEINS

Our discussion properly begins with the subject of proteins, because for our purpose, which is essentially a study of race, and therefore heredity, proteins are the most important. In nucleated cells it is conjugated

protein which carries the hereditary characteristics. Chromosomes consist largely of nucleoprotein. By analogy, nucleoprotein may be believed to carry the hereditary characteristics in non-nucleated forms. Proteins are highly complex and infinitely variable. Uniting them with nucleic acid to form nucleoprotein must confer further biological individuality upon them. Therefore, in an effort to separate forms of life on a chemical basis, a knowledge of their proteins and particularly nucleoproteins is of the most value.[4]

1. Simple Proteins and Amino Acids: Little systematic investigation of the proteins proper of the tubercle bacillus has been made. It is believed that at least half of the bacilliary body is in the form of protein, and it is known that some of this is in the conjugated form combined with nucleic acid. Probably some is conjugated with sugar as glycoprotein

TABLE 1

Amino acid content of tubercle bacillus protein

	TAMURA	JOHNSON AND BROWN
	per cent	*per cent*
Total nitrogen	100	100
Basic nitrogen	11.85	37.63
In arginine	7.64	10.63
histidine	1.53	11.48
lysine	1.49	3.69
ammonia	1.15	11.83 (amide)
Monoamino acid nitrogen	66.59	47.39
Humin nitrogen	15.79	4.11

also, but this has not been well worked out. The nature of the protein present is also obscure. Some work indicates that albumen and globulin may be present, and Ruppel claimed that he found a protamine, but the results lack confirmation—as well as refutation.

More attention has been paid to the cleavage products of the proteins. Tamura (5) in 1913 and Johnson and Brown (6) recently, have published analyses of the tubercle bacillus for amino acids. These differ considerably, however, as shown by table 1. High percentages of the monoamino acids, phenyl alanine and valine, were conspicuous findings of Tamura, while the histidine figure of Johnson and Brown is noteworthy.

As a matter of fact, there is nothing highly characteristic of the amino acid content of plant proteins or animal proteins. The proteins of sperm

[4] For a very interesting article on the evolution of the proteins the reader is referred to Kennaway, *Chemical News*, 1920, cxx, 13.

heads, which are unusually rich in the diamino acids, particularly arginine, constitute an exception to this statement. It is commonly found, also, that vegetable proteins have a high content of glutaminic acid. Furthermore, occasionally they lack one or more of the common amino acids entirely, but this is true of some animal proteins also. The glutaminic acid content of the tubercle bacillus has not been determined. The amino acids which are occasionally lacking in proteins, as lysine and tryptophan in zein, and tyrosine in gelatin, are all present in the tubercle bacillus. Only one common protein is known to have as high a histidine content as that reported by Johnson and Brown for the tubercle bacillus. This is the animal protein globin (from hemoglobin) (7). The similarity here may be coincidental, but calls for more work on this important point. In general, it may be said that there is nothing known in the character of tuberculoprotein which would relate it particularly to one type or the other.

2. *Conjugated Protein and Nucleic Acid:* On the other hand, the best evidence we have at present for classifying the tubercle bacillus in either group comes from the analyses of tuberculinic acid, the nucleic acid of the tubercle bacillus. The knowledge here referred to we owe to the recent researches of Johnson and Brown (8). For proper understanding of the significance of their results a few words are necessary concerning the chemistry of nucleic acid. A full treatment will be found in the monograph on this subject by Walter Jones (9). A half century of research, following the pioneer investigations of Miescher on nuclein, has established the fact that α-nucleic acids are well defined compounds of characteristic composition, into which the following substances regularly enter: phosphoric acid, a carbohydrate and two purine bases and two pyrimidine bases. Furthermore, the tendency of modern research is to recognize but two α-nucleic acids, in view of the fact that the best analyses of nucleic acids reported seem to identify all of them with one or the other of two types, of which yeast-nucleic acid and thymus gland-nucleic acid, respectively, are representative members. The following schematic representation of the composition of these two acids, taken from Levene and Jacobs (10) (11), shows the differences in their make-up:

Yeast nucleic acid	*Thymus nucleic acid*
Phosphoric acid-pentose-guanine	Phosphoric acid-hexose-guanine
Phosphoric acid-pentose-adenine	Phosphoric abid-hexose-thymine
Phosphoric acid-pentose-uracil	Phosphoric acid-hexose-cytosine
Phosphoric acid-pentose-cytosine	Phosphoric acid-hexose-adenine

It is seen that the two acids are similar in structure, but display two important differences: (1) the carbohydrate linkage, between the phosphoric acid on the one hand and the characteristic bases on the other, is in the case of the yeast acid a *pentose*, and in the thymus acid a *hexose;* and (2) the pyrimidine base *uracil* appears in the yeast nucleic acid and not in the thymus form, while the pyrimidine base *thymine* appears in the thymus but not in the yeast acid.

"These two nucleic acids," says Jones,

> are the best known members of two sharply defined groups into which all substances of this class may be divided, and indeed there is a well formed and constantly growing opinion among physiological chemists that all nucleic acids are identical with one or the other of these two compounds. . . . . If such literature with its unavoidable errors be reviewed in the light of our most recent knowledge, all confusion disappears, and we come to understand that there are but two nucleic acids in nature, one obtainable from the nuclei of animal cells, and the other from the nuclei of plant cells. In examining the evidence one naturally takes into consideration that experimental exactness in such a field is entirely out of the question and that concurrent tendencies are all that can be reasonably demanded.

The chief objection to these conclusions is that the number of nucleic acids so far examined is small. In the group designated as *plant nucleic acids* we have but two well investigated members, which indeed seem identical; these are *yeast nucleic acid* and the nucleic acid of the wheat embryo, *tritico nucleic acid.* In the animal group a larger number have been extensively investigated, including thymus, pancreas, spleen and various kinds of sperm acids. Until we have a larger representation of well analyzed members of the plant group, agreeing in their make-up with the analyses of the present well investigated forms, the significance of bacterial analyses with respect to plant and animal classification will naturally be subject to some doubt.

However, on the basis of present existing knowledge and belief, we have definite evidence permitting us to classify tuberculinic acid. Johnson and Brown, working with 803 gm. of dry tubercle bacilli in two lots,[5] one of which consisted of human tubercle bacilli and the other of bovine and human types mixed, *isolated 7.7 gm. of pure nucleic acid, which on acid hydrolysis yielded cytosine and thymine but no uracil.* Since the

[5] Supplied by Parke, Davis & Co. and the H. K. Mulford Company, as byproducts of tuberculin manufacture.

publication of their article, Brown, who is continuing the study, has repeated the investigation on 810 gm. of dry bacilli with identical results.

Tests to ascertain the nature of the sugar present indicate that this answers every qualitative test for a hexose and not a pentose. It is to be mentioned that Bendix (12) obtained, on the hydrolsis of tubercle bacilli and also on hydrolysis of the nucleoprotein obtained from them, a reducing substance which yielded an *osazone* and an *orcin* addition product which were apparently of the pentose type. Brown's product, however, that is to say, *nucleic acid as pure as modern methods will make it*, freed from all protein and extraneous matter, yields formic and levulinic acid and only a small amount of furfuraldehyde on acid hydrolysis. This result speaks for the presence of a hexose, not a pentose.

The other constituents of the nucleic acid of the tubercle bacillus have been isolated and identified. The phosphorus constitutes 8.2 per cent of the acid, according to a figure obtained by Brown on a part of his material. This is not far from the figure of 8.9 per cent demanded by the Steudel and Levene and Jacobs formulas. Long (13) isolated both *adenine* and *guanine* in almost equal quantities and could not find any other purines present.

Altogether, while no attempt to determine the configuration of the several substances isolated from tuberculinic acid has been made, enough work has been done to indicate that the usual constituents of a nucleic acid are all present, and that these substances are such that tubercle bacillus-nucleic acid corresponds with the animal type and not the plant. However vague and confusing other data with regard to the phylogenetic classification of the bacillus may be, this one fact stands out with exceptional clearness. It should be added that no other bacterial nucleic acid has been so well investigated.

CARBOHYDRATES

Unfortunately, no systematic study of tubercle bacillus carbohydrates comparable to the investigation of the nucleic acid has been made. As mentioned above, monosaccharides are constituents of nucleic acid itself, and a discussion, concerning that part of the carbohydrate of the tubercle bacillus entering into the composition of nucleic acid, is given above. Besides this moiety, sugar-like substances are to be found in several other fractions of the tubercle bacillus. Carbohydrate is probably present as part of protein molecules, as part of lipin molecules, and also in un-

combined form. Agulhon and Frouin (14) obtained from tubercle bacilli a phosphatid which they believed to belong to the class of jecorins, as it liberated on hydrolysis, besides fatty acid, glycerol and a base analogous to *choline*, a gummy polysaccharide from which glucose split off on further hydrolysis. This finding has not yet been confirmed by repetition. This compound will be referred to again in the discussion on phosphatids below.

One of the best means for differentiating plant and animal forms should be found in the field of the polysaccharides. As a matter of fact we are almost uninformed as to the type of compound of this class present. To be sure there are reports of substances of the soluble glycogen-inulin type, and again there are claims for the presence of such insoluble polysaccharides as cellulose and the nitrogenous "carbohydrate" chitin, a polymer of glucosamine. Of the substances mentioned, a content of glycogen or of chitin would speak for an animal form, while the presence of inulin or cellulose would relate the microögranism quite definitely to the plants.

There is an old report of a compound like glycogen in the body of the bacillus. Levene (15) extracted a substance which remained in solution after removal of nucleic acid and protein. It gave an opalescent solution in water, and could be precipitated with alcohol and basic lead acetate. With iodine it gave a color test similar to that obtained with glycogen. It did not reduce Fehling's solution directly but did so after acid hydrolysis.

Panzer (16) has also reported the presence of a water-soluble polysaccharide. He extracted a substance free from phosphorus, nitrogen and sulphur, which gelatinized on cooling. It was precipitated by alcohol and lead acetate and reduced Fehling's solution after hydrolysis. The substance failed to liberate mucic acid on hydrolysis (test for galactose) and was therefore not a galactan. Physically, it resembled gum arabic, which is a pentosan, and, it should be added, a peculiarly plant substance. The hydrolysate gave the Molisch α-naphthol test, but this is of no significance in distinguishing pentoses from hexoses. Panzer's material was far from sufficient to enable him to tell whether the substance was really made up of pentoses or not, and apparently no attempt to determine this was made.

More ambitious was the study of Tamura (17), who also, and with much more evidence, concluded that pentosans were present. His experiments were made with the tubercle bacillus and also with an acid-

fast saprophyte, *Mycobacterium lacticola*. After separation of fatty substances, and as complete removal as possible of the proteins, he had left a substance which was insoluble in alkali, insoluble in ammoniacal copper solution (Schweitzer's cellulose reagent), failed to give the iodine reaction for chitin, and was easily hydrolyzed by 3 per cent sulphuric acid, the hydrolysate reducing Fehling's solution readily and giving the orcin hydrochloride test for pentoses. An osazone was obtained from the *Mycobacterium lacticola* material, which on analysis gave figures corresponding to the pentose arabinose. The tubercle bacillus product, which resembled the mycobacterium product in all other respects, was insufficient for this test. From these results Tamura concluded that chitin and cellulose were absent, and that he was dealing with a hemicellulose or pentosan.

These results furnish a strong argument for the vegetable nature of the bacillus, as pentosans are typically plant products. However, several objections must be made to Tamura's conclusions, with due recognition of the excellence of the work done. In the first place, aside from the fact that his best figures come, not from the tubercle bacillus, but from the *Mycobacterium lacticola* material, his yield of carbohydrate was very low. His biggest yield was from mycobacteria, defatted but not treated for removal of proteins. From 50 gm. of dry bacterial body he obtained 0.1 gm. of what appeared to be *arabinose hydrazone*. Granting that his product was truly a pentose, it must still be admitted that this quantity could be locked up in some other combination than pentosan. So, too, the defatted, alkali-treated material, referred to in the preceding paragraph, was not necessarily pentosan merely because it contained pentose. Tamura himself states that by alkali treatment it was impossible to free it completely from protein. Pentoses, which were first found in the animal kingdom, are present in β-nucleic acids, such relatively simple compounds as the guanylic acid of the pancreas, and perhaps elsewhere. Clinicians will be reminded of this fact in the Cammidge test for diseases of the pancreas, and the occasional occurrence of persistent pentosuria in man. The significance of Tamura's findings is thus not sharp, but it must be admitted that they are important and that they constitute the best evidence available to-day for classifying the tubercle bacillus with the plants on the basis of chemical composition.[6]

[6] Baudran (18) claimed that he found true cellulose in the tubercle bacillus, but his contention is based largely on a color reaction and is not convincing.

The search for carbohydrates of characteristically animal nature has led to practically negative results. To be sure Helbing (19) compared the acid-fastness of the tubercle bacillus to that of the shell of certain taenia eggs known to contain chitin, and suggested that the acid-fastness of the tubercle bacillus might be due to chitin. No experimental proof accompanied the suggestion, however. On the other hand, definite attempts to isolate *glucosamine*, the characteristic hydrolytic product of chitin, have failed (20).

Thus, summing up our knowledge on the carbohydrates of the tubercle bacillus, we find the best evidence to be in favor of a classification in the plant world. The evidence is meagre enough, however, and objection can be raised to all of it. The situation distinctly calls for more work, and until that is forthcoming, here, in this unsettled way, the case must rest.

LIPINS

1. Wax and Alcohol: The lipin content of the tubercle bacillus has undoubtedly been more extensively investigated than all the other fractions together. The strikingly high lipin content was impressive to the earliest observers. A critical examination of the known facts might throw light on the question here under consideration. The 30 to 40 per cent of the bacillary substance which is soluble in such reagents as ether, chloroform, ligroin and toluene, includes some free fatty acids, some fats, some phosphatids, but chiefly (60 to 70 per cent, Long and Campbell (21)) a waxy substance which is an ester of fatty acids with an alcohol of high molecular weight. It is upon this wax that interest has chiefly centered, and its nature is by no means yet revealed. The tendency is to accept Tamura's analysis (5) as probably the closest approximation on record. This observer believed it to be the lauric acid ester of an alcohol of the composition $C_{29}H_{55}OH$. There are indications that other acids than lauric are present, however.

What light does the presence of this compound shed on the problem which we are discussing? Bürger (22) believes that the lipin resembles plant waxes, and points out that such cerolipoids occur commonly in the tissues of xerophytic plants and are protective in nature. However, he adduces no evidence to show that the characteristic part of tubercle bacillus wax, that is, the alcohol or sterol (solid alcohol) part, resembles phytosterols more than zoösterols, if we may introduce the latter term. It appears to be indeed true that the commonest animal sterol, choles-

terol, is absent from the tubercle bacillus, but the physical similarity of mycol (tubercle bacillus—and probably other bacterial—sterol) to cholesterol is close enough to have kept the search for the latter in the bacillary substance active for some time. Certainly, substances similar to mycol are widely distributed through the animal kingdom. Czapek (3), in his comparison of plant and animal sterols, is able to present no chemical means of classifying them in two groups. He describes differences between individuals of the two series, such as in melting point and crystalline form, but there appears to be nothing absent from one group and holding good throughout the other, which would serve for differentiation of unknowns. Altogether, important as it is in the make-up of the tubercle bacillus, mycol furnishes us with no basis whatsoever for plant or animal distinction.

2. *Phospholipins:* Phospholipins are widely distributed throughout nature and are not absent from the tubercle bacillus. As is well known, phospholipin problems are among the most difficult in all physiological chemistry. It is only in the last few years, thanks largely to the brilliant work of MacLean and Levene and their associates, that order is at last coming out of chaotic confusion. Even yet, perfect agreement as to the chemical composition of the best known and best studied members of the group is by no means reached. The battle still rages over the actual existence of other substances. The reason for this lies in the extreme difficulty in purifying bodies of this class and in their instability.

Claims in the field of phospholipins, to be convincing, must be based on repeated observation, rigid purification of material and a wealth of chemical experience, in addition to the obvious requirement of original capacity on the part of the investigator. This means years of work and an abundance of material. It is small wonder then, that much significance cannot be attached to the few isolated observations concerning the slow-growing tubercle bacillus in this difficult domain. There are several observations on record, however, and these might be of much significance as to the problem in hand, could we take them at their face value.

Before considering these claims, a few words should be said concerning the distribution of phospholipins in nature. First isolated from animal tissues they were generally thought of as animal products until, after a time, reports of "plant lecithins" began to be made. Since then it has come to be believed likely that substances of this general class are pres-

ent in all cells, in which they play important rôles in oxidation and also in cell permeability. However, there is still a more or less widely spread impression that although the number of main groups of phospholipins is not large, small differences within the molecule may go far toward conferring biological individuality.

Widely distributed as plant phospholipins may be, and complex and variable as subsequent research may prove them, it is unquestionable that they reach their greatest development and are present in greatest proportion in the most animal of all animal tissues, the central nervous system. It is here that they are most easily obtained in quantity and have been most extensively and most creditably investigated. The finding in the tubercle bacillus of lipoids like the brain lipoids can, at least, never support the hypothesis of plant affiliation.[7] Whether or not it supports the animal hypothesis depends upon two things: first, upon the certainty of the correctness of the finding and, second, upon what future research tells us concerning the existence of the same compounds in the plant world.

The most recent reported investigation of the lipoids of the tubercle bacillus, which should have had the advantages of modern knowledge, is that of Koganei (23) of Tokyo. Unfortunately, in this report the chain of reasoning is most difficult to follow. A few short analyses lead to the abrupt, unexplained conclusion that *phrenosin*, *kerasin*, *sphingomyelin* and *kephalin* are present. A fair sample of the character of the work is seen in the claim for the presence of sphingomyelin on the basis of a 1:1 nitrogen-phosphorus ratio, and the fact that on baryta hydrolysis only choline and phosphoric acid went into solution. The identification of the base is most gravely open to question. The addition of platinum chloride to the hydrolysate caused a precipitate "which showed definitely the presence of choline." Without going deeply into the chemistry involved, it suffices to say that many things besides choline are precipitated by platinum chloride, that choline and phosphoric acid could just as well be split off from egg lecithin by his method, and finally that the N:P ratio in sphingomyelin is not 1:1 but 2:1.

The identification of kephalin is equally lucid and convincing. A substance admitted by the author to be four-fifths impurity gives nitro-

[7] An able plant physiologist, who has had the kindness to look this paper over and delete its most glaring mistakes, makes the following comment on this sentence, "The botanist would insist that the discovery of such compounds in fungi (including bacteria) would establish the presence of compounds of this class in plants."

gen and phosphorus figures which signify that "there is no doubt about the presence of kephalin." The acid-fastness of the tubercle bacillus is rashly but definitely attributed to kephalin, and the author concludes triumphantly with the statement that the four substances phrenosin, kerasin, sphingomyelin and kephalin have never before been recorded as constituents of tubercle bacilli.

It is unfortunate that effort has not been more wisely expended in this field. The importance of the phospholipins warrants the most intelligent consideration. It is perhaps not exceeded by that of the well known wax.

A finding which may have some slight bearing on the problem is that of Agulhon and Frouin (14), who isolated a compound hydrolyzing into glycerol, fatty acids, a base analogous to choline, and a gum which on further hydrolysis yielded glucose. The substance was classified as a *jecorin*, from its similarity to the jecorins so widely distributed in animal tissues. Jecorins probably have no status as chemical units. They are now believed to be simply mixtures. The difficulty of removing sugar and other impurities from the phosphatids, especially from the kephalin of the brain, is well known. It should be mentioned that phosphatids from which sugar can be separated only with difficulty have been isolated and studied in plants by Winterstein and Hiestand (24).

Altogether, in going over the literature of tubercle bacillus chemistry, I find only one article on phospholipins in the bacillus to which I am willing to attach significance. Tamura (5), whose other contributions have several times been referred to above, in the course of his investigation of the tubercle bacillus in Kossel's laboratory, precipitated with acetone and carried through some stages of purification a substance which gave, with more than fair accuracy on two trials, a nitrogen-phosphorus ratio of 2:1. There is no doubt that modern technique would demand a more rigid purification than Tamura carried out and not two analyses but many. However, incomplete as it is, it represents the best analysis of a tubercle bacillus phosphatid that we have. It suggests the presence of sphingomyelin or a related compound. Sphingomyelin appears to have a wide animal distribution. Levene has obtained closely agreeing figures with products from brain, kidney, liver and egg yolk. Whether or not it has plant distribution remains for future research to show.

3. Fatty Acids: We do not need to devote much space to these compounds. What knowledge we have is fairly definite. *Palmitic acid* was found in the bacillus by the early investigators. This acid has a wide distribution in both kingdoms. *Oleic acid*, also found, likewise characterizes neither. *Lauric acid*, on the other hand, which Goris (25) and others have found in tubercle bacilli, appears to have a wider distribution in plants than in animals, deriving its name from its abundance in the laurel berry. Beilstein's *Handbook* may be consulted for a summary of the vegetable substances in which it is found. It occurs also in many animal products, although apparently in most instances simply as a result of its presence in the animal's diet, with absorption and storage in unchanged form. In such fashion, also, we may readily explain its presence in milk. For our present purposes the type of fat in a given substance is significant only if the fatty acids were synthesized there. In tubercle bacilli grown on glycerol-broth the lauric acid, which the researches of Goris (25) and others have found in considerable quantity, must have been synthesized by the bacilli. The same may be said of the plant fatty acid, *crotonic acid*, which Goris claims exists in a glassy product from the bacillus, which he designates *hyalinol*.

Lauric acid occurs in some animal products, in which its presence is not so readily explained as a dietary sequel; for instance, in spermaceti, the wax obtained from the skull cavity of the sperm whale. It is interesting that in this substance lauric acid exists in a combination similar to that found in tubercle bacilli, namely, as the wax-like ester of an alcohol of high molecular weight. Such facts are sufficient to withhold us from including the presence of lauric acid among the definite plant characteristics.

METABOLISM

It is partly on the basis of metabolism that the tubercle bacillus and other bacteria have been generally classified among the plants. An ability to exist on simple compounds, and transform these readily into complex protoplasm, is supposed to be one of the distinguishing attributes of vegetable life. If the tubercle bacillus were not heterotrophic, and were able to withdraw carbon dioxide from the air and grow with this as its sole source of carbon, there would be little or no opposition to placing it forthwith among the plants. An examination of the known facts of its metabolism will show that the situation is not so simple.

Several distinctive features of the metabolism are known and fairly well understood. Some of these have been discussed in these pages before.

1. Nitrogen Metabolism: The tubercle bacillus, like the majority of bacteria, will thrive when nitrogen is furnished in very simple form. So far from requiring ready-built proteins, proteoses or peptones, it can satisfy its nitrogenous needs with amino acids, or a single amino acid if necessary, or, finally, even with ammonia alone. It synthesizes purine bases and the cyclic amino acids when the only nitrogen supplied is ammonia (13). It is helpless only when its nitrogen supply is limited to nitrates, nitrites or elemental nitrogen. This capacity has been considered peculiarly plant-like, and it must be admitted that the synthesis of proteins from ammonia and organic matter is one of the great functions of plant life. This endowment, with its sister one of reducing carbon dioxide, saves the living world from inevitable decay. But that it is peculiar to plant life is another matter. It is unquestionable indeed that the higher forms of animal life take their nitrogen in a more complex state than ammonia: amino acids and a considerable variety of them, are usually required. Conversely, they could not live, were they rationed with ammonia as their sole source of nitrogen. However, it is not so certain that they are unable to synthesize amino acids or use ammonia at all. Certainly, one amino acid can be liberated in the body of herbivora in huge quantity, probably in excess of any possible stored amount and must therefore be synthesizable. I refer to the liberation of *glycine* under the stress of detoxicating large amounts of benzoic acid. In addition, I think it has been satisfactorily demonstrated that the reaction by which the amino acid *alanine* is broken down into pyruvic or lactic acid and ammonia is a reversible one, namely, that the amino acid can be synthesized from these substances by the tissues of even the fastidious mammalian body. Embden and Schmitz (26) were able to recover alanine (in excess of that formed by autolysis) after perfusion of the isolated liver with ammonium pyruvate, and demonstrated a similar synthesis with ammonia and several oxyacids. This evidence is cited, not with the intention of suggesting that such a process is a common type of metabolism, but simply to prove that, far removed as they are from plant forms, some, at least, of the mammals have retained from some distant ancestor's possessions what must have been a fundamental property, that of synthesizing very simple nitrogenous

substances into complex ones. On the whole, the extensive capacity manifested by the tubercle bacillus in the utilization of nitrogen is unlike anything commonly seen in the order of higher animals and quite like that seen in both the lowest and highest plants.

Ammonia may also be looked upon as an excretory product of the tubercle bacillus. Recognized plants similarly break down their own proteins and liberate some ammonia. But this is no distinctive property. Animals, including man, possess it. Prone as they are to excrete nitrogen in some more complicated form, as urea or uric acid, under certain conditions, particularly the necessity of neutralizing acid, higher animal organisms, as well as lower, are capable of liberating considerable amounts of ammonia from their tissues.

2. Carbon Metabolism: I have said that the capacity for synthesizing complex compounds from very simple substances is characteristically a plant one. The green plants need only nitrates for nitrogen, carbon dioxide for carbon, and water and certain salts, to carry on existence. The higher animals practically require, in addition to water and the same salts, amino acids for their nitrogen, and make extensive use of sugar and fats. As far as carbon utilization is concerned, the tubercle bacillus is unique in one way. Of course, devoid, as it is, of chlorophyl, it makes no use of carbon dioxide. But it is particular in its requirements beyond this. As is well known, most sources of carbon do not satisfy the bacillus. It will utilize certain sugars slowly, and I have seen it propagate feebly and for a limited period on certain acid amides; but for steady and luxuriant growth, what we may call normal growth, glycerol is essential. It seems to function partially in forming the wax in which the bacillus is so rich. It seems to me that this inflexibility, this failure to be satisfied with the simple acids, such as acetic, propionic, glyoxylic, lactic or pyruvic acid, or a simple alcohol, like ethyl alcohol, which, by the way, do support many bacteria, is very interesting, but it offers no means for distinction from the heterotrophic plants.

Little needs to be said about the energy production of the tubercle bacillus; it resembles that of both plant and animal cells in that carbonaceous compounds are oxidized. Its carbon excretion, like that of all cells, is partly in the form of carbon dioxide. In addition it excretes organic acids, or perhaps forms them from the constituents of the medium, which in the "take and leave" mode of existence of unicellular forms is

analogous to the excretion of higher forms. Both plant and animal forms do this also abundantly.

A discussion of metabolism could not be closed without some reference to the vitamins, the growth accessory substances. It has been sometimes said that for plants vitamins are unnecessary and that for animals they are required. At present we are by no means sure that plants do not need them too, for continued growth. The tubercle bacillus requires more study before we can definitely state the situation with it. I have tried with commercial vitamin preparations to increase its rate of growth, and have not succeeded. On the other hand, I have repeatedly grown the bacillus in simple media containing no trace of vitamin. But it must be remembered that inoculation of media with the tubercle bacillus must always be generous. Furthermore, it is a fact that, so far from becoming adapted to growth on simple media, cultures tend to run out and ultimately stop growing if repeatedly transferred on simple, so called synthetic media. May this not be the result of an ultimate failure of vitamin? Certainly, it is doubtful if, in its vitamin relation, the tubercle bacillus displays definite plant leanings.

SUMMARY AND CONCLUSIONS

From the arguments advanced above it is at once apparent that, seen from the chemical point of view, the tubercle bacillus exhibits recognized plant tendencies and recognized animal ones. Summarized they are about as follows:

Fairly definite

For the animal:

It contains a typical nucleic acid of the animal type, probably identical with that of thymus, pancreas, sperm and spleen. It does not contain nucleic acid of the so called plant type found in yeast and wheat. The basis for these statements lies in the established presence of the pyrimidines, thymine and cytosine, in tubercle bacillus nucleic acid, and the presence of a hexose, and the established absence of the pyrimidine uracil.

For the plant:

It possesses marked chemosynthetic power in nitrogen metabolism. synthesizing such complex substances as amino acids and purine bases with no other source of nitrogen than ammonia.

Less definite

For the animal:

It is said to possess lipins of the diamino-monophosphatid type, which so far have been described convincingly only in animals.

For the plant:

It is said to contain hemicellulose or pentosans, made up of pentose units, which are typical plant substances. An appreciable content of the fatty acid, lauric acid, which has a wide plant distribution, has also been recorded.

The question may well be raised of whether it is futile to attempt to decide the question on a basis so full of conflict. The answer is that out of such an exposition of known facts, as has been attempted above, some distinctions might be found presenting possibilities for arbitrary classification. The situation in organic chemistry is recalled and the purely arbitrary but highly useful classification into great divisions on the basis of the presence or absence of carbon. I have no intention of settling the matter in this paper. For me the question remains open, until such time as future research furnishes a basis on which a distinction, purely arbitrary perhaps, may be made. I confess to the hope that in the nucleic acids such a distinction may be ultimately found. It is Johnson and Brown's finding in the tubercle bacillus of what present day research definitely characterizes as an animal nucleic acid that prompts this survey of the whole field. But I realize that the present distinction of nucleic acids as of plant and animal types rests on a slender foundation. The finding of a nucleic acid identical with tubercle bacillus nucleic acid in a pumpkin seed, for instance, would wreck my hope. On the other hand, should chemical research continue to find "plant nucleic acids" only in unquestioned plants and "animal nucleic acids" only in what are by common consent animals, I would regard the tubercle bacillus finding as one of great evolutionary significance.

I am frankly doubtful, however, whether the situation will ever prove so simple. Biological variation of protoplasm means differences, not only in constituents, but also in their relations. As Levene (27) puts it, "Specificity, individuality or character may be brought about not by single substances, but rather by definite and constant equilibria of substances." E. B. Wilson (28) writes, "When we speak of protoplasm as the physical basis of life we mean simply the sum total of all the sub-

stances that play any active part in cell life." We shall know where to put the tubercle bacillus in the kingdoms of nature when we have learned not only its composition but the interrelations of its elements. We have much to learn; but in the meantime it is to the credit of those who have added to our knowledge of the chemistry of the tubercle bacillus that they have put on record for this bacillus far more than has been done for any other bacterium.

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CHAULMOOGRA OIL IN THE TREATMENT OF LARYNGEAL TUBERCULOSIS[1]

OBSERVATIONS ON ITS LOCAL AND CONSTITUTIONAL EFFECTS

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The frequency with which larygneal tuberculosis complicates the course of pulmonary tuberculosis has caused many laryngologists and phthisiologists to devote considerable time to the study of therapeutic possibilities for this affection. Owing to the accessibility of the larynx for examination and local medication, a large number of remedies have been advocated and in due time discarded. Since laryngeal tuberculosis is, in most instances, but a local manifestation of increased pulmonary disease, as was well emphasized by Dworetzky (1), it follows that the former disease is subject to the same remissions that are so characteristic of pulmonary tuberculosis. It is thus possible that improvement is often ascribed to a given drug when in reality it is due to the improvement in the pulmonary focus. When the latter is stationary, the laryngeal disease, as a rule, also remains stationary, either with or without treatment, as was shown by us elsewhere (2).

Chronic tuberculous laryngitis does not therefore present any problem of consequence, as the majority of cases without ulceration do not suffer from any symptoms other than dryness, huskiness of voice or actual aphonia, and perhaps the vague sensation of a lump in the throat. These symptoms vary in extent, constancy and relation to one another to such a degree, that even the patient comes to look upon the affection as a symptom-complex of pulmonary tuberculosis, necessitating no other treatment than that prescribed for the primary disease. On the other hand, the peracute, acute and subacute types of laryngeal tuberculosis constitute a most formidable problem, for the appearance of pain and dysphagia, alone, at once gives rise to a vicious cycle that leaves only disaster in its wake.

Among the numerous palliative remedies there is not one capable of affording continuous relief from the distressing symptoms, and the use of the galvanocautery is prohibited in acute cases. The infiltration of

[1] From the Sanatorium of the Jewish Consumptives' Relief Society, Sanatorium, Colorado.

the superior laryngeal nerve with alcohol gives only occasional relief. Lukens's favorable report on the value of chaulmoogra oil in relieving pain and dysphagia (3) was therefore received enthusiastically by those who are called upon daily to treat this disease. The success obtained with this oil in the treatment of leprosy, as reported by Morrow and his associates (4), further stimulated interest and study of this drug, in view of the probable familial relationship between the causative agents of leprosy and tuberculosis.

During the first two months of our observation of a group of 50 cases, we followed Lukens's method of injecting the various strengths of the oil intratracheally or intralaryngeally. At that time we chanced to learn of the work of Corper and Freed (5) which was then in progress. The acute pneumonic consolidations, localized abscesses or chronic proliferative inflammations in animals injected intratracheally with chaulmoogra and other oils could not be questioned, and Corper (6) demonstrated clearly the readiness with which liquids injected intratracheally were aspirated into the finer alveoli, where the insoluble particles remained for a long time and gave rise to inflammatory lesions. Simon (7), in discussing Corper's researches from a clinical standpoint, pointed out the singular fact that, while it was practically impossible to obtain aspiration of fluids into the lungs after nasal instillation in rabbits and dogs when the animals were in the horizontal posture, aspiration invariably occurred in animals in the upright posture.

A problem in the therapeutics of laryngeal tuberculosis, heretofore not thought of, became crystallized. The possibility of damage to lung tissue from the use of any oil, applied to the larynx, either by the syringe method or the atomizer, was carefully considered; for, as a rule, the patient, at the time of treatment, is instructed to breathe quietly, not to swallow or expectorate the medication and to inhale the drug when used through a spraying atomizer—procedures most favorable for aspiration.

In connection with the possible untoward effects upon the pulmonary parenchyma from the use of such powders as iodoform, orthoform, anesthesin, etc., the articles of Heiman and Ashner (8) and Goldbloom (9) were recalled. These authors reported acute bronchopneumonias in children from accidental inhalation of zinc stearate; and Heiman and Ashner produced a similar condition in dogs by forcibly insufflating talcum powder into the trachea with a DeVilbiss powder blower. The

analogy drawn by us was that, if accidental inhalation of the powder could produce a pneumonic process, how much more is it likely to develop from the continuous and purposeful inhalation of such irritating powder as iodoform?

It became obvious that a more extensive study over a prolonged period of time would be necessary, in order to be able to solve the entire problem; but, since a study of the effects of one drug upon the lungs when used intratracheally or intralaryngeally might enable us, by comparison, to determine in a measure the effects of other drugs, it was decided to continue the work with chaulmoogra oil. A careful clinical and roentgenological study was thus undertaken to ascertain, if possible, not only the local effects of the drug, but also the effects upon the lung from possible aspiration.

It might be argued that roentgenoscopy is too crude a method to detect the finer changes in lung tissue, especially when one has to deal with organs already extensively diseased. This point was strongly emphasized by Corper (10); but one cannot deny that roentgenograms, if capable of demonstrating miliary tubercles, should also show new areas of consolidation presumptively a good deal larger than miliary tubercles. Amberson (11), in discussing the value of the roentgenogram in the study of pulmonary pathology, asserts that "by means of serial roentgenograms the mutations of destruction and repair may be depicted at desired intervals for months or years. The evidence is not microscopic, but no other art can ever reveal as much of the macroscopic data as this form of biopsy examination."

Clinical evidence of acute pneumonic consolidation should be expected in every case. It is true that extensive changes in the lungs can take place without giving rise to symptoms. Pneumokoniosis and chronic fibroid phthisis are good examples; but it must be remembered that the pulmonary changes noted in the latter diseases occur gradually, extending over a period of many years, whereas in inflammatory conditions caused by aspiration the process is acute and is accompanied by fever, rapid pulse, dyspnea, etc. Physical signs, elicited by auscultation, should also be taken into account in summarizing the results of the observations.

Before proceeding with further investigation it became necessary to determine whether or not oils, injected into the larynx by the usual methods practised by the laryngologist, are actually aspirated into the

bronchi and thence into the alveoli. No doubt was entertained on that point when the tracheal cannula was introduced beyond the vocal cords, but such a method was considered too radical a procedure, in view of the dangers of massive aspiration. It was therefore decided to use only the intralaryngeal method; yet, even with the latter method it was noted that with the patient in the sitting posture and head extended, the oil, when dropped upon any of the laryngeal structures, except the epiglottis, would gravitate toward the vocal cords and, during phonation, pass beyond the cords into the trachea. Additional evidence was deduced from the fact that the location of the sense of tingling or burning following the use of chaulmoogra oil was invariably referred to the midsternum and at times as low down as the xiphoid cartilage. Very rarely was cough excited by this procedure. Those cases that had nausea or vomiting had no sensation of burning in the areas mentioned, and the conclusion was that in the latter group of cases the oil was swallowed and not aspirated.

Reference to the appended tables will show the methods pursued in this investigation. It will be seen that 50 cases were treated. Forty-three were treated with chaulmoogra oil and observed for a period of twelve months, and 7 were treated with ethyl esters of the oil, kindly supplied to us by the Winthrop Chemical Co. under the trade name *Chaulmestrol*. The latter group of cases was observed for ten months. Both oils were given in increasing strengths, beginning with 5, 10, 25 and 50 per cent, mixed with pure liquid petrolatum. As tolerance was acquired the pure oil was administered.

Table 4 shows that the total amount of oil used was over 1000 cc. and the average amount given to each patient was 20 cc., during an average period of a little over four months. The length of treatment must not be confused with the length of clinical observation which, as already stated, was from ten to twelve months. While the average patient received only 20 cc. of the chaulmoogra oil and 18 of the *Chaulmestrol*, there were a number of cases who received as much as 40 cc. One case received 28 cc. of the pure chaulmoogra oil.

To obviate the possibility of error in the interpretation of the end results, the various parts of the observation were assigned to different physicians. One of us made the laryngeal diagnosis prior to treatment and did not examine the larynx again until the treatment was discon-

tinued. The physical examinations of the chests and the roentgenographic studies were not made by the same physician who treated the larynx. The possibilities of prejudice or overenthusiasm was thus eliminated to a great extent.

Table 1 shows the types of tuberculous laryngitis, and table 3 describes in detail the pathological changes of the individual structures. It will be noted that of the 50 cases, 9 had acute tuberculous laryngitis, 23 were subacute, 17 were chronic and 1 had a normal larynx. The latter case was used as a control to determine the irritating effect, if any, of the drug upon the normal mucous membrane. No change was noted. The proportion of acute cases in this series was unusually large. It is also noteworthy that 43 cases had ulceration of one or more structures; consequently, pain and dysphagia were prominent symptoms.

The laryngeal diagnosis was slightly changed at the end of the treatment. Four cases of the subacute group showed a tendency to chronicity, while 2 cases previously classified as subacute and chronic, respectively, became acute. In studying the changes of the individual laryngeal structures, progressive pathological changes were noted in 12 or 24 per cent, improvement in 3 or 6 per cent and a stationary condition in 35 or 70 per cent. The progressive cases showed a spread of the ulceration or infiltration. In one case the right vocal cord, apparently normal prior to treatment, assumed the typical "mouse-eaten" appearance. In this case, and in seven others of the progressive group, the pulmonary lesion remained stationary; hence, the progressive laryngeal lesions could not be ascribed to progressive pulmonary tuberculosis. In a recent report on a group of 139 cases under no treatment other than a spray of 1 per cent mentholated liquid petrolatum, the authors (2) recorded only 8 cases of progressive laryngeal involvement. It is very plausible, therefore, to assume that chaulmoogra oil has some irritating properties and probably was a factor in causing the spread of local ulceration.

The possibility of error in studying the effects of a given drug on laryngeal symptoms has already been pointed out. Symptoms such as dryness, slight radiating pains or the sensation of fulness in the throat are ephemeral; they may be very annoying one day and absent the next, without any demonstrable change in the larynx. In this group of cases no record was made of improvement unless such improvement continued for at least two weeks or longer. Analysis of table 2 will show that in 56 per cent of the cases the symptoms were unaffected, in 23

per cent aggravated and in 21 per cent improved. Complete relief from pain was noted in only 2 cases, and relief from dysphagia in one. Those 3 cases were of the chronic type. In none of our acute cases was there any symptomatic improvement. The disappearance of such symptoms as dryness or dysphonia could not be attributed to the oil, as such symptoms frequently improved without any local medication. The pure oil was employed in acute cases with marked pain and dysphagia, using the laryngeal applicator when no results were obtained from the syringe method, and repeating the treatment daily, without any appreciable effect upon the symptoms.

It must be pointed out here that while the drug is believed to possess irritating properties, as judged by the subjective sensation of burning, particularly in cases with ulcerations, no local evidence of irritation, such as increased hyperemia, was noted in any of the cases, even from the continuous use of the pure oil, although progressive ulceration was more marked when the 50 per cent or the pure oil was used.

In considering the clinical course, it is realized that not in every case could changes be attributed with certainty to the use of the drug. It is only by careful analysis and close observation that some deductions can be made, and even then the possibility of error is not to be overlooked.

Table 5 shows the pulmonary diagnosis before and after treatment. It will be seen that, with one exception, the 7 moderately advanced inactive cases continued to be inactive during the treatment and throughout the period of observation. Of these 7 only one had to be classified far advanced after treatment. Practically all of the progressive cases were derived from the far advanced group, 28 of whom had other extrapulmonary complications. Of the 20 progressive cases, 18 ran a progressive course prior to treatment. The 2 cases that became worse during treatment manifested typical tuberculous symptoms, such as increased cough and expectoration, and fever not above 100°F. Physical signs elicited a spread of the lesion over one or more interspaces and no activity at the bases. In fact, none of this group of cases showed increased involvement of the bases. This is important, for in the event of aspiration, the lowermost portions of the lungs should be expected to share the major part in the inflammatory reaction, because of gravity and the greater suction action of the lower halves of the lungs.

The main interest in the clinical part of this report is the fact that under treatment 16 per cent improved and 44 per cent remained stationary. This was corroborated by taking into account the various individual symptoms, such as cough, expectoration, weight, streaked sputum, temperature, etc., as can be seen from table 6. The clinical course corresponded fairly well with the symptoms and the roentgen plates. This would tend to prove that in man there is apparently no danger from the intralaryngeal use of oils, as no evidence of acute inflammatory pulmonary foci or new areas of pulmonic consolidation could be obtained by the usual clinical methods. It is possible that the drug, when aspirated, is later expelled in the sputum. According to Bullowa and Gottlieb (12) the peristaltic action of the bronchial muscles is as important a factor in the emptying of the lung and bronchi as the ciliary movement of the bronchial mucous membrane. Whether this is true of oily globules cannot be answered satisfactorily, although one must assume that some definite mechanism must exist whereby the lung can rid itself of insoluble particles, even when aspirated deep into finer bronchioles or alveoli; for, in the absence of such a mechanism, every one of our cases should have developed pneumonic comsolidation. In one terminal case 16 cc. of the pure oil were injected intratracheally during a period of sixteen days. Necropsy failed to disclose macroscopic evidence of new areas of pneumonic consolidation, although round cell infiltration around the oil globules was noted, as will be reported later.

In making the comparative roentgen study an attempt was made to use the same technique in every case. Only 39 cases had comparative plates, and of these 8 showed improvement, 18 revealed no changes and 13 showed a spread of the lesion. The changes noted can be seen from the following:

Progressive:	
Increased infiltration and cavitation, upper lobes	3
Increased cavitation	1
New cavitation, upper lobe	1
Increased basal radiation	1
Increased infiltration, upper lobe	7
Improvement:	
Decreased mottling	3
Increased fibrosis	4
Contraction of apical cavities	1

From the above it can be seen that among the progressive cases only one showed a probable basal involvement, while in the others the new

involvement was in and around the areas of disease noted prior to the treatment. A comparison between the clinical course and the roentgen findings will show that of the 18 cases considered stationary, from a roentgenological standpoint, 6 were clinically progressive; but in each of these 6 cases there were extrapulmonary complications that were sufficient to account for the loss in weight, persistent fever, etc. The pulmonary symptoms were not increased, and physical examination of the chests did not disclose evidence of a spread of the lesion.

To illustrate the clinical course of some of the cases, a few brief reports, selected from the progressive, stationary and improved groups are briefly presented:

Case 8: M. D., age twenty-five, male, tailor, admitted October 1, 1921. Pulmonary symptoms since December, 1920; chiefly cough and expectoration and periodic attacks of fever, 99° to 100°, lasting three to five days and occurring about once a month. Physical signs showed dulness in both upper lobes from the 2nd rib and 4th dorsal spine, with a few subcreptitant râles between the 1st and 3rd ribs on the left side. Laryngoscopic examination showed the presence of ulcerating granulations at the posterior commissure, infiltration of both arytenoids and ulceration of the left vocal process. The chief laryngeal symptoms were dryness, sensation of fulness in the throat and radiating pains. Treatment with chaulmoogra oil was begun on March 27, 1922, and discontinued September 1, 1922. A total of 35 cc. in various strengths was used. Five treatments consisted of the pure oil, after which increased ulceration was noted in the interarytenoid space, although the pain seemed less annoying. The physical signs in the chest did not change, and the patient was afebrile during the entire period of treatment. Comparative roentgen plates disclosed no changes. The sputum was negative on ten examinations and once positive, one month after the treatment was started. Weight on admission, 153 pounds; present weight, 155 pounds.

Case 14: G. G., male, age twenty-one, weaver, admitted October 7, 1921. Pulmonary symptoms since May, 1917. Chief complaints on admission were cough, excessive expectoration, dryness and soreness of throat, and occasional difficulty in swallowing and weakness. Examination of the chest disclosed evidence of infiltration through the greater part of both lungs, with cavitation in both upper lobes. The chief changes in the larynx consisted of ulcerations in the interarytenoid sulcus and infiltration of both arytenoids. Treatment was started on March 16 and discontinued September 16. A total of 16 cc. of the oil was used. The general condition became much improved, as evidenced by lessened cough and expectoration and decreased moisture in the

chest. The laryngeal symptoms were changing daily, but there seemed to be less infiltration of the arytenoids at the end of treatment. The sputum was consistently positive. Weight on admission, 124 pounds; present weight, 125 pounds. The last X-ray plate shows increased fibrosis.

Case 18: N. L., male, age twenty-six, clerk, admitted July 28, 1922. Pulmonary symptoms since June, 1921. Course chronic with occasional febrile reactions not above 100°F., lasting two to three days. *Chest examination:* Dulness and bronchovesicular breathing with subcrepitant râles on both sides from the 3rd rib and 6th dorsal spine. The chief laryngeal changes were ulceration of commissure and right cord. Chief symptoms, dryness and dysphonia. Treatment began August 8 and was discontinued November 16. A total of 18 cc. of 25 per cent of the oil was used. No effect was noted on the pulmonary or laryngeal symptoms. The temperature was normal throughout. Physical signs revealed more subcrepitance, especially on the left side. The X-ray plate showed increased mottling in the upper halves of both lungs. Sputum was Gaffky II on admission and the last report stated "sputum contains innumerable tubercle bacilli." Weight on admission, 121 pounds; present weight, 128 pounds. Patient is ambulant and afebrile.

Case 20: J. T., female, age twenty-six, bookkeeper, admitted March 21, 1922. Pulmonary symptoms since February, 1921. Persistent hoarseness, slight dysphagia and occasional pain since onset of the disease. Chest signs: Right side, dulness and bronchovesicular breathing from 3rd rib and 5th dorsal spine with many subcrepitant râles. Left side, dulness and bronchovesicular breathing from 1st rib and 2nd dorsal spine, no râles. Laryngoscopic image showed extensive ulceration of the entire interarytenoid space and right vocal cord. Treatment began April 1 and was discontinued November 1. A total of 36 cc. of the oil was used, 18 cc. of which was pure. During the first 2 weeks the temperature fluctuated between 98° and 99.6°F., and later it was normal throughout the period of observation. No change in the chest signs was noted on November 28, except a slight increase in moisture on the right side and a few subcrepitant râles at the left apex. No improvement in the laryngeal symptoms or the local lesion. Sputum on admission was Gaffky II and on discharge Gaffky VI. Weight on admission was 130 pounds and on discharge 145 pounds. Comparative roentgen plates showed no changes.

Case 32: S. W., male, age twenty-two, furrier, admitted November 8, 1922. Onset of disease with laryngeal symptoms in August, 1922, consisting of dysphonia, dysphagia and pain. Chest examination disclosed extensive infiltration of right upper lobe and slight involvement of left apex. Subcrepi-

tant râles were heard over those areas. The larynx showed extensive infiltration and ulceration of epiglottis and left arytenoid. A few scattered tubercles could be seen on posterior pharyngeal wall. Treatment was begun at once and continued daily to December 25. A total of 22 cc. of the pure oil was used. During the first week the patient was afebrile, but since then the temperature has been fluctuating daily between 99° and 101°. Chest signs are unchanged and the last roentgen plate discloses no gross changes. The general course is progressive and there has been a loss of 15 pounds in weight. The dysphagia had to be controlled by cocaine and later by nerve infiltration. The local ulceration has spread, involving now the right arytenoid and left vocal cord.

Case 38: S. F., male, age 37, admitted July 16, 1921. Onset of disease with laryngeal symptoms in March, 1921, consisting of dysphagia and pain. Examination on admission revealed active pulmonary tuberculosis involving the greater portion of the left lung and right upper lobe. Extensive ulceration of the arytenoids and the left vocal band were the chief laryngeal changes. The patient was afebrile and the laryngeal lesion seemed to pursue a chronic course. Cauterization relieved the dysphagia. The patient left of his own accord July 26, 1921, with general condition unimproved. Readmitted August 4, 1922, in a moribund state. Extreme dysphagia, especially for fluids. Physical and roentgen examination revealed extensive bilateral pulmonary tuberculosis, with cavitation in the left upper lobe. The larynx showed extensive ulceration of all structures, and the cords could not be seen. Treatment was started the next day. A total of 16 cc. of the pure oil was used in a period of sixteen days. The intratracheal method was employed. Failing to obtain relief, additional pure oil was applied to the ulceration with the applicator, without any relief. Death occurred August 28 and the necropsy disclosed no macroscopic areas of acute pneumonic consolidation. The report of the histological studies, made by Drs. Corper and Freed of the research department of the National Jewish Hospital reads as follows: "Sections of the lung tissue submitted were stained with the scarlet red method. Oil globules were visible in the diseased, but not caseous, tissue; the oil was also seen in the alveoli. The tissues showed a response in the form of round cell infiltration around the oil globules, but not comparable in degree of reaction obtained in normal rabbits. In the latter, the response is very distinct and consists of pneumonic consolidation quite a distance from the oil globules. Some oil globules did not seem to have produced infiltration. That may be explained by the recent injection. The difference in reaction between the rabbit and the human lung is only that of degree. This may be due to the possibility that lungs diseased with miliary tuberculosis, as in this case, do not respond as strongly to insoluble particles as lungs of normal

animals. The caseating material also took the fat stain, but the stain was paler and of more dust-like distribution than that of chaulmoogra oil. No difficulty was experienced in differentiating between the two kinds of fat-staining substances." Unfortunately, no comparative plates were made in this case.

Case 40: A. S., male, age 26, tailor, admitted April 12, 1922. Onset of pulmonary symptoms in the Spring of 1920. Physical examination disclosed evidence of infiltration of both upper lobes with subcrepitant râles over the left upper lobe. The chief laryngeal changes were ulceration of both vocal cords with infiltration of both arytenoids. Laryngeal symptoms, aphonia and dysphagia. Course prior to treatment afebrile. Prior to the special treatment, the patient was treated every other day with formalin and mentholated oil. Chaulmoogra oil treatment began May 5, 1922, and was discontinued November 20, 1922. A total of 38 cc. of the oil, in strengths ranging from 5 to 50 per cent, was used. The entire clinical course was unmodified. Slight improvement in the voice was noted. The pathological condition of the larynx remained unchanged. The roentgen plate after the treatment shows no gross changes, except a contraction of a cavity on one side and almost the total disappearance of a cavity on the other side. Weight on admission, 131 pounds; present weight, 130 pounds. Sputum positive on admission and negative on the last two monthly examinations.

SUMMARY

Fifty cases, 12 with moderately advanced and 38 with far advanced pulmonary disease, presenting varying degrees of laryngeal tuberculosis, were observed over a period of ten to twelve months, while under local treatment with chaulmoogra oil and the ethyl esters of the oil. No difference in the action of the two drugs was noted. There was neither an aggravation of the local symptoms as reported by Peers and Shipman (13) nor any improvement as observed by Lukens (3) and Alloway and Lebenson (14). The increased local ulceration noted in a number of cases could not be attributed to any other cause than to the irritating effects of the drug. Evidence of its irritation was also deduced from the fact that a number of cases complained of burning, deep in the chest, and referred the pain to the midsternum or xiphoid. Progressive pulmonary cases continued to run a progressive course, while most of those with stationary pulmonary lesions remained unchanged. The pulmonary symptoms and the general clinical course were unmodified. The slight variation in the course and symptoms, as depicted in detail in the

tables, are common characteristics of phthisis and cannot be ascribed to the use of the oils. In no instance did the cough become diminished or the expectoration less tenacious in character. A follow-up study, with serial roentgen plates in 39 cases, failed to disclose satisfactory evidence of new or recent pneumonic consolidation or new areas of infiltration such as could be caused by aspiration.

CONCLUSIONS

1. Chaulmoogra oil has proved of no therapeutic value in our series of cases with laryngeal tuberculosis.

2. Its local use may cause progressive ulceration.

3. No acute pneumonic consolidation resulted from the intralaryngeal use of the oil, as could be determined by ordinary methods.

4. No clinical or roentgen evidence could be obtained to prove the existence of an acute active proliferation in the lungs as a result of the aspiration of the oil, although such a process probably was present in some cases, as was evidenced by the necropsy findings in one case.

5. Further clinical studies are necessary to determine whether or not the use of the oils and powders applied to the larynx through the atomizer, insufflator or syringe have any injurious effects upon the lungs.

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TABLE 1

Laryngeal diagnosis

LARYNGEAL DIAGNOSIS	LARYNGEAL DIAGNOSIS PREVIOUS TO CHAUL-MOOGRA OIL	LARYNGEAL DIAGNOSIS AFTER CHAUL-MOOGRA OIL	LARYNGEAL DIAGNOSIS PREVIOUS TO "CHAUL-MESTROL"	LARYNGEAL DIAGNOSIS AFTER "CHAUL-MESTROL"
Acute tuberculous laryngitis	7	9*	2	2
Chronic tuberculous laryngitis	14	17†	3	3
Subacute tuberculous laryngitis	22	17	1	1
Normal (control)			1	1
Total	43	43	7	7

* 1 previous subacute, 1 previous chronic.

† 4 previous subacute.

TABLE 2

Effect of treatment upon laryngeal symptomatology

LARYNGEAL SYMPTOMS BEFORE TREATMENT	LARYNGEAL SYMPTOMS AFTER TREATMENT								STATIONARY	IMPROVEMENT	PROGRESSIVE	TOTAL
	None	Unchanged	Partially relieved	Aggravated	Dryness only	Dryness pain only	Dysphonia relieved	Dysphonia dryness only				
Dryness	2	2							2	2		4
Dryness, pain	1	3	1						3	2		5
Dryness, fullness		2		1	1			1	4		1	5
Dryness, dysphonia		2							2			2
Dryness, dysphonia, fullness		1							1			1
Dryness, pain, irritation				1							1	1
Dryness, pain, dysphonia		8			1		2		8	3		11
Dryness, pain, fullness	1	1							1	1		2
Pain		1							1			1
Pain, dysphagia, fullness	1									1		1
Pain, dysphonia, fullness		1							1			1
Pain, dryness, dysphagia, dysphonia		1		7		1			1		8	9
Pain, dryness, dysphagia, dysphonia, fullness				2							2	2
Pain, dryness, dysphonia, fullness		1							1			1
Fullness		1							1			1
Burning		1							1			1
None	2								2			2
Total	7	25	1	11	2	1	2	1	29	9	12	50
Percentage	14	50	2	22	4	2	4	2	58	18	24	

TABLE 3

Effect of treatment upon laryngeal pathology

LARYNGEAL PATHOLOGY	STATIONARY	IMPROVEMENT	PROGRESSIVE	TOTAL
Infiltration and ulceration of commissure	16		1*	17
Infiltration of arytenoids and ulceration of commissure	6		1†	7
Generalized infiltration of all structures	5	2		7
Infiltration of all structures and ulceration of commissure	2			2
Ulceration of commissure and left cord			1	1
Ulceration of commissure, arytenoids and left cord	1		1	2
Infiltration and ulceration of right band, commissure of right cord			1	1
Infiltration of bands, arytenoids and ulceration of commissure			1‡	1
Ulceration of commissure and infiltration of bands	1			1
Ulceration of commissure and right cord and infiltration of arytenoids	2			2
Ulceration of arytenoids and commissure and infiltration of bands and cords	1			1
Epiglottis, infiltration and ulceration			3	3
Epiglottis, commissure, infiltration and ulceration			1	1
Epiglottis, commissure, arytenoids, infiltration and ulceration			1	1
Epiglottis, miliary tubercles, infiltration, arytenoids and ulceration of commissure		1		1
Extensive ulceration of all structures			1	1
Normal	1			1
Total	35	3	12	50
Percentage	70	6	24	

* Increased granulation.

† Increased infiltration.

‡ Ulcerated cords.

TABLE 4

Treatment

MODE OF TREATMENT	NUMBER OF PATIENTS TREATED	AMOUNT OF OIL GIVEN	AVERAGE AMOUNT OF OIL GIVEN PER PATIENT	AVERAGE NUMBER OF MONTHS TREATED	AVERAGE NUMBER OF TREATMENTS RECEIVED PER PATIENT	LARYNGEAL COURSE PREVIOUS TO CHAULMOOGRA OIL OR "CHAULMESTROL"				LARYNGEAL COURSE AFTER TREATMENT WITH CHAULMOOGRA OIL OR "CHAULMESTROL"			
						Improved	Stationary	Progressive	Total	Improved	Stationary	Progressive	Total
		cc.	*cc.*										
Chaulmoogra oil	43			4.16	20.31		22	4	26		20	6	26
5 per cent.		17	0.395										
10 per cent.		274	6.37										
25 per cent.		338	7.86										
50 per cent.		82	1.90										
100 per cent.		171	4.00										
Total		882	20.52										
"Chaulmestrol"	7			2.57	18.2		5	2	7		5	2	7
5 per cent.		1	0.14										
10 per cent.		24	3.42										
25 per cent.		28	4.00										
50 per cent.		23	3.28										
100 per cent.		52	7.42										
Total		128	18.26						33				33
Treatment previous to chaulmoogra oil or "Chaulmestrol":													
Formalin	6			2.5		Cases treated	6		6	1	5		6
Cautery	6			1.5		with chaulmoogra oil	3	3	6		3	3	6
Cautery, formalin	4			7			3	1	4	2	1	1	4
Cautery, formalin, heliotherapy, lactic acid	1			9			1		1		1		1
Number of previous treatments	33								17				17

TABLE 5

	PULMONARY DIAGNOSIS																CLINICAL COURSE			
	M. A. Active				M. A. Inactive				F. A. Active							F. A. Inactive				
	Turban II				Turban II				Turban III							Turban III				
	R^1L^1	R^1L^2	R^2L^1	Total	R^1L^1	R^1L^2	R^1	Total	R^2L^2	R^1L^3	R^2L^1	R^2L^2	R^2L^3	R^3L^3	Total	R^2L^2	Total	Improved	Stationary	Progressive	Total
Previous to chaulmoogra oil treatment	3	2	1	6	4	1	1	6	8	3	4	2	7	6	30	1	1	7‖	21	15	43
After chaulmoogra oil treatment	2	2	1	5	4	1	1	6	8*	3†	4	1	7§	8¶	31	1	1	7‖	19 △	17 □	43
Previous to "Chaulmestrol" treatment	1			1	1			1	2	2		1			5				4	3	7
After "Chaulmestrol" treatment					1			1	1	2	2‡	1			6				4	3	7

* One previous M. A. active R^1L^1.

† One previous F. A. active R^2L^2.

‡ One previous M. A. active R^1L^1; one previous F. A. active R^2L^2.

§ One previous F. A. active R^1L^3.

¶ One previous F. A. active R^3L^2; one previous F. A. active R^2L^2.

‖ Two cases pneumothorax.

△ Previous progressive.

□ Four previous stationary.

TABLE 6

Study of the effect of chaulmoogra oil and "chaulmestrol" upon pulmonary symptoms

	COUGH					EXPECTORATION					HEMOPTYSIS				TEMPERATURE				WEIGHT					GASTRIC SYMPTOMS			
	None	Slight	Moderate	Excessive	Total	None	Slight	Moderate	Excessive	Total	None	Streaked sputum	Present	Total	Normal 98°	Moderate 99°–101°	Excessive above 101°	Total	Stationary	Increased	Loss	No record	Total	None	Diarrhea, cramps	Neurotic	Total
Previous to chaulmoogra oil treatment	1	5	23	14	43	1	3	33	6	43	38	3	2	43	25	13	5	43	19	13	8	3	43	33	5	5	43
After chaulmoogra oil treatment		10	20	13	43	2	5	30	6	43	38	3	2	43	25	15	3	43	19	13	8	3	43	32	6	5	43
Previous to "Chaulmestrol" treatment		2	4	1	7		2	5		7	4	2	1	7	6		1	7	2	3	2		7	6	1		7
After "Chaulmestrol" treatment		2	4	1	7		2	4	1	7	5	1	1	7	4	3		7	2	3	2		7	7			7

TABLE 7

Comparison of roentgen findings and clinical course

	COMPARISON OF ROENTGEN PLATES BEFORE AND AFTER TREATMENT			TOTAL	NUMBER OF NO COMPARATIVE PLATES	TOTAL	GRAND TOTAL
	Improved	Stationary	Progressive				
Chaulmoogra oil	7	16	11	34	9	9	43
"Chaulmestrol"	1	2	2	5	2	2	7

Clinical course

	Chaulmoogra oil	"Chaulmestrol"	Chaulmoogra oil	"Chaulmestrol"	Chaulmoogra oil	"Chaulmestrol"		Chaulmoogra oil	"Chaulmestrol"	Total	
Improved	4		2		1					7	
Stationary	3	1	8	2	2			6	1	23	
Progressive			6		8	2		3	1	20	
Total	7	1	16	2	11	2		9	2	50	50

TABLE 8

Comparative table

	LARYNGEAL SYMPTOMS			LARYNGEAL PATHOLOGY			LARYNGEAL COURSE			CLINICAL COURSE			PULMONARY SYMPTOMS			ROENTGEN FINDINGS		
	Improved	Stationary	Progressive	Improved	Stationary	Progressive	Improved	Stationary	Progressive	Improved	Stationary	Progressive	Improved	Stationary	Progressive	Improved	Stationary	Progressive
Chaulmoogra oil, per cent	20.9	56	23.1	7	69.9	23.1	7	69.9	23.1	16.3	44.2	39.5	23	42	35	20.6	47	32.4
"Chaulmestrol," per cent		71	29		71	29		71	29		57	43		71	29	20	40	40

THE THERAPEUTIC AND BACTERICIDAL VALUE OF ORGANIC MERCURIAL COMPOUNDS IN EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS[1]

STUDIES ON THE BIOCHEMISTRY AND CHEMOTHERAPY OF TUBERCULOSIS. XXVIII

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In 1921 I published a report of my earlier work on over twenty compounds of mercury and their value in the chemotherapy of experimental tuberculosis (1). In this report the earlier literature on the subject was quite exhaustively reviewed. Any further review of the early literature on mercury seems unnecessary at this time.

Most of the compounds used in my earlier work were commercial preparations, bought on the market, some being inorganic and a few organic. A few were double salts of mercury with a dye, which were made for me by my chemical assistants after published methods. For some years before 1921 and ever since that time, several chemical assistants have been investigating for me the problem of making organic mercury compounds, with the special purpose of combining mercury with methylene blue to make a stable soluble compound, which should be more efficient than the double salts of methylene blue and mercuric chloride reported in the article referred to above. In connection with this investigation a considerable number of organic compounds of mercury with various compounds of phenol and of aniline were made. The methods of making these compounds have been described by them in the chemical literature (2) and will not be given in this report. The inhibitory power of these compounds on the growth of human tubercle bacilli *in vitro* was first tested and the report of the results was published in 1922 (3). The inhibitory power of compounds having mercury in various positions in the benzene ring and also the effects of various groups substituted in different positions were compared. It was found that certain of these compounds completely inhibited growth of the

[1] From the Otho S. A. Sprague Memorial Institute and the Department of Pathology, University of Chicago.

tubercle bacilli in dilutions up to 1 in 100,000, while phenol itself inhibited only at 1 to 1000 and mercuric chloride at 1 in 40,000. The compounds having high inhibitory power were selected for therapeutic treatment of tuberculous guinea pigs and also for bactericidal experiments.

In this way, seven compounds of phenol and six of aniline were chosen for the work to be reported in this paper. The bactericidal power of these compounds was tested in the following manner:

A suspension of a very virulent human tubercle bacillus, 4015, from H. J. Corper's laboratory, was made in physiological salt solution, containing in each cubic centimetre 1 mgm. moist weight of the culture of 4015 grown for three weeks on glycerol-agar. To 10 cc. of this suspension were added sufficient amounts of the compounds to be tested to make dilutions 1 in 1000, 1 in 10,000 and 1 in 100,000. After thorough shaking of each flask, they were put in the incubator at 37.5°C. for one hour and twenty-four hours. At the end of each such time, 1 cc. was withdrawn and added to 10 cc. of physiological salt solution and well shaken. One-half cubic centimetre of this dilution was then injected subcutaneously into each guinea pig, three animals being used for each time, each dilution and each compound. Hence each guinea pig received a dose of 0.05 mgm. of the culture of tubercle bacilli. Controls were made in the same way, physiological salt solution being used instead of the drug. Only five of the thirteen compounds selected for therapeutic use were tested for their tuberculocidal power.

Table 1 gives the names and chemical formulae of these compounds and the results of the experiment as to the distribution of the disease in the four organs most generally affected in the tuberculous guinea pig. Three pluses indicate involvement of the organ in all three animals tested, while minuses indicate no extension of the disease to that organ. From this table it may be seen that mercuric chloride, though much lower in inhibitory power than any of the organic mercurials listed in the table, showed slightly higher tuberculocidal power than any except 14 M, while number 20 and P-nitroso phenol O-mercuric chloride, caused considerable lowering of virulence, as indicated by the degree of distribution, even at 1 in 100,000. Only with P-nitroso phenol O-mercuric chloride did one hour's exposure affect the distribution of the infection even at a concentration of 1 in 1000. O-nitro phenol P-carbinol O-mercuric acetate, the inhibitory efficiency of which extended to 1 in 100,000, showed the least tuberculocidal action.

TABLE 1

COMPOUNDS	ORGANS	1 TO 1,000		1 TO 10,000		1 TO 100,000	
		1 hour	24 hours	1 hour	24 hours	1 hour	24 hours
$HgCl_2$	Lymph nodes	+++	−−−	+++	−−−	+++	+++
	Spleen	+++	−−−	+++	−−−	+++	+++
	Liver	+++	−−−	+++	−−−	+++	+++
	Lungs	+++	−−−	+++	−−−	+++	+++
14 M	Lymph nodes	+++	−−−	+++	−−−	+++	+++
	Spleen	+++	−−−	+++	−−−	+++	+++
	Liver	+++	−−−	+++	−−−	+++	+++
	Lungs	+++	−−−	+++	−−−	+++	+++
No. 20	Lymph nodes	+++	−−−	+++	+++	+++	+++
	Spleen	+++	−−−	+++	+−−	+++	+−−
	Liver	+++	−−−	+++	+−−	+++	−−−
	Lungs	+++	−−−	+++	+−−	+++	+−−
P-Nitroso Phenol O-Mercuric chloride	Lymph nodes	++−	−−−	+++	+−−	+++	+−−
	Spleen	+−−	−−−	+++	−−−	+++	+−−
	Liver	+−−	−−−	+++	−−−	+++	−−−
	Lungs	+−−	−−−	+++	−−−	+++	−−−
Na No. 15	Lymph nodes	+++	+−−	+++	+++	+++	+++
	Spleen	+++	+−−	+++	+++	+++	+++
	Liver	+++	−−−	+++	++−	+++	+−−
	Lungs	+++	+−−	+++	+++	+++	++−
O-Nitro phenol P-Carbinol O-mercuric acetate	Lymph nodes	+++	+++	+++	+++	+++	+++
	Spleen	+++	+++	+++	+++	+++	+++
	Liver	+++	+++	+++	+−−	+++	++−
	Lungs	+++	+++	+++	+++	+++	+++
Control	Lymph nodes	+++	+++				
	Spleen	+++	+++				
	Liver	+++	+++				
	Lungs	+++	+++				

THERAPEUTIC EXPERIMENTS

Series 1: The animals of this series were inoculated January 15, 1920, subcutaneously, with 0.05 mgm. of 1305, a strain of human tubercle bacilli of moderate virulence. Eight of the animals of the series were kept untreated as controls and the others were divided into sets, with 8 guinea pigs in each set, and treated with the organic mercury compounds named below. The guinea pigs were fed 1 to 2 mgm. per day, the feeding

and the dosage being regulated according to the weight of the animal which was taken once a week. They also received weekly subcutaneous injections for a time, but these caused severe infiltrations, necrosis and ulcerations, and were therefore discontinued.

The following mercurial compounds were used in treatment of the guinea pigs in this series:

(1) *Number 9:* Sodium P-nitrophenol O-mercuric chloride, an isomer of mercurophen, having 52.8 per cent, of mercury and inhibiting the growth of tubercle bacilli *in vitro* in dilutions up to 1 in 100,000. The animals of this set lived 52, 100, 120, 176, 187, 224 and 276 days, or an average of 162 days, and received 45, 86, 106, 200, 220, 297 and 372 mgm., or an average of 189.4 mgm. for each. In several of the animals death was due to an acute suppurating infection and in none was the tuberculous involvement very extensive. In all some lymph glands were slightly enlarged but not caseous. The involvement of the spleen, liver and lungs was very slight.

(2) *Number 15:* Mercuri-bis-P-nitrophenol. This contains 42 per cent of mercury which forms a bridge between two nitrophenol rings. It prevents the growth of tubercle bacilli *in vitro* in dilutions to 1 in 100,000, but failed to kill all the bacilli in twenty-four hours, even at 1 in 1000. The 8 guinea pigs died after 7, 25, 26, 31, 31, 68, 159 and 224 days, the first 5 dying of acute infections and showing no tuberculosis. The other three received 63, 180 and 400 mgm. of the compound and showed very little or no tuberculosis.

(3) Dimethyl aniline P-mercuric acetate, having 52.8 per cent mercury. The compound completely inhibits in dilutions to 1 in 20,000 to 1 in 40,000. The maximum duration of life was 117 days and the average 95 days. All showed extensive involvement of lymph nodes, liver, spleen and lungs. Apparently, there was no beneficial effect from treatment with this aniline mercury compound.

(4) Symmetrical P-mercury dimethyl aniline, containing 45.8 per cent of mercury which forms a bridge between two dimethyl aniline rings.

This position should, according to Abelin (4), render the compound less toxic than most of the other organic mercurials, although perhaps also less active. This compound was quite insoluble in water and the subcutaneous injection of it suspended in oil caused much infiltration, necrosis and ulceration. The animals lived 25, 119, 125, 146 and 150 days, or an average of 113 days, having received by mouth 24, 106, 112,

129 and 160 mgm. of the drug, or an average of 106 mgm. per animal. All the animals except the first showed marked tuberculous involvement of lymph nodes, spleen, liver and lungs.

The 8 untreated controls of this series lived 14, 66, 66, 207, 213, 270, 277 and 301 days, or an average of 155 days. The two which died first died of acute infections, with very little tuberculous involvement. All the others showed marked and extensive tuberculous involvement of lymph nodes, spleen, liver and lungs. Hence, the controls of this series lived as long as or longer than the treated animals, though some of the treated animals showed much less extensive distribution of the disease.

Series 2: November 1, 1920, a second series of guinea pigs was inoculated subcutaneously with 0.0002 mgm. of number 4015, isolated a few months earlier by Dr. Corper, and said by him to be of such virulence that 0.00001 mgm. caused a slowly progressive tuberculosis, generalizing after about three months. The dose used by me caused generalized infection in about five weeks and the untreated controls died after 8, 22, 45, 63, 70, 84, 84 and 112 days, all except the first two showing generalized infection, the lymph nodes, spleen, liver and lungs being usually involved. The other guinea pigs of this series were treated by daily feeding of pills, each containing from 1 to 2 mgm. of the following organic mercury compounds. Weights were taken once a week to determine the condition of the animals and their ability to continue the treatment.

(1) *Number 15:* 2, 2′ Mercuri-bis-P-nitrophenol. This compound had 42 per cent of mercury and inhibited growth in dilutions to 1 in 100,000. It killed all bacilli only in dilutions of 1 to 1000 at twenty-four hours. These animals died after 3, 60, 78, 86, 88 and 99 days. All except the first showed generalized tuberculosis, lymph nodes, spleen, liver and lungs being usually involved.

(2) Saligenin dimercuric acetate or phenol O-carbinol 2, 4 mercuric acetate, a compound made and kindly sent to me by Dr. Hirschfelder of the University of Minnesota, and containing 45.5 per cent of mercury. The animals treated with this compound died after 15, 24, 36, 36, 56, 60, 135 and 176 days, or an average of 67 days. They had received 12, 21, 26, 26, 37, 40, 116 and 151 mgm. All except the first two had generalized tuberculosis, although in most acute infections had been contributory factors in their death. However, there was no indication that this compound had had any beneficial effect on any of the animals.

(3) P-nitroso phenol O-mercuric chloride, having 55.9 per cent of mercury and inhibiting in dilutions up to 1 in 100,000. The animals treated with this compound lived 4, 35, 53, 57, 58, 59, 61 and 64 days, or an average of 49 days. While an acute intestinal infection contributed much as a cause of the early death, all except the first to die showed some tuberculosis, mostly generalized.

(4) *Number 26:* M-nitro dimethyl anilin P-mercuric acetate, which has 47.2 per cent mercury and inhibits up to 1 in 100,000. This set lived 20, 36, 45, 47, 59, 74, 113 and 263 days, and received 17, 25, 30, 33, 45, 58, 92 and 204 mgm. of the compound. All showed some tuberculosis and all except the first two showed it widely distributed.

(5) *Number 27:* Dimethyl O-nitro aniline P-mercuric acetate, has 47.2 per cent mercury and inhibits up to 1 in 100,000. The guinea pigs treated with this compound lived 30, 30, 32, 32, 44, 48, 92 and 98 days, and received 20, 22, 22, 33, 37, 75 and 81 mgm. of the drug. While the first four died from subcutaneous suppuration, intestinal infection or pneumonia and had very little tuberculosis, the others all had extensive involvement of glands, spleen, liver and lungs.

(6) *Number 29:* Monomethyl P-nitraniline O-mercuric acetate, has 48.8 per cent mercury and inhibits growth of tubercle bacilli *in vitro* up to 1 in 100,000. This set showed very marked intestinal affections and all died within 44 days, yet all showed some tuberculosis and in most cases it was fairly well generalized.

(7) *Number 14 M:* Mono-ethyl P-nitraniline O-mercuric acetate, has 47.2 per cent mercury, inhibits growth up to 1 in 100,000, and has stronger tuberculocidal action than any of the other organic mercurials and equal to that of mercuric chloride. The acute intestinal and pulmonary affections prevailed among these guinea pigs also, but all lived long enough to develop some generalized tuberculosis, though the maximum duration of life was 57 days.

(8) *Number 20:* 2, 2′ hydroxy 4-nitroso-mercury diphenyl, with mercury at 48. 2 per cent and forming a bridge between the two phenyl rings. This has an inhibitory power ranging from 1 in 100,000 to 1 in 300,000, but its tuberculocidal action was not so great as that of *number 14 M*. The animals treated with *number 20* lived 39, 39, 47, 48, 51, 57, 60 and 104 days, having received 34, 34, 38, 38, 41, 46, 49 and 87 mgm. of the compound. The first four showed slight tuberculosis of lymph nodes and spleen, while the last four showed marked tuberculosis of these and liver and lungs also.

Series 3: Series 3 was inoculated January 18, 1921, with 0.025 mgm. of 1305. The object of this third series was to test the efficiency of these compounds in slowly progressing chronic tuberculosis of guinea pigs, since it was noted in my earlier report (1) that some drugs had a much more pronounced effect in chronic than in acute tuberculosis, and that this chronic tuberculosis in guinea pigs resembled more nearly human tuberculosis than does the more usual acute form. The untreated controls of this series showed no generalized tuberculosis after 76 days, but after 98 days lymph nodes and spleen were involved. The animals dying after 451, 556 and 656 days showed very marked tuberculosis of lymph nodes, spleen, liver and lungs, while one which lived 706 days showed no tuberculosis and no scars of healed tuberculosis.

The animals were divided into sets, 6 guinea pigs to each set. One set was kept as controls, while the other sets were treated each with one of the following organic mercurial compounds. Each guinea pig was fed daily a bread pill containing 1 mgm. of the drug for 11 days, after which 2 mgm. were fed. In the earlier part of the experiment they were also anointed with an oil containing 2 per cent of the same drug. They were weighed once a week and, if the weight was found materially decreased, the feeding was stopped for a week and then resumed, but there was very little necessity for interrupting the treatment in this series. The urine of a number of the animals was collected at intervals and examined by the Elliott method (5) for mercury. It always gave a positive test, showing that the compound is taken up by the blood and excreted by the kidneys. Several treated animals that died after long treatment with these drugs had their organs examined qualitatively for mercury after administration of total amounts varying from 27 to 577 mgm. Spleen, liver, kidneys and lungs all generally showed from a trace to a very distinct reaction, though in no case was there a weighable amount. The amount was estimated at about 0.1 mgm. in the organs by comparison with a test made on the organs containing a known amount. The spleen seemed to contain the largest amount, though the kidney was a close second.

The compounds used were as follows:

(1) *Number 26:* M-nitro dimethyl anilin P-mercuric acetate. This inhibits growth of tubercle bacilli completely up to a dilution of 1 in 100,000. These lived 140, 186, 350, 433, 475 and 610 days after receiving 176, 222, 356, 573, 651 and 1176 mgm. of the drug. All of these except the one that died after 433 days showed some general tuberculous in-

volvement, though in most cases very slight. The one exception showed no tuberculosis whatever.

(2) *Number 27:* O-nitro dimethyl anilin P-mercuric acetate. These lived 31, 93, 132, 173, 336 and 512 days, having received 46, 124, 157, 205, 473 and 775 mgm. of *number 27*, in addition to the amount absorbed from the anointing with 2 per cent oil suspension. The first and third of the animals to die showed no tuberculosis except slightly involved regional lymph nodes. All the others showed greater or less involvement of lymph nodes, spleen, liver and lungs, the involvement being about the same as in the untreated controls, so that apparently there was no beneficial effect from treatment from this compound.

(3) *Number 29:* P-nitro monomethyl anilin O-mercuric acetate. These lived 38, 342, 384, 512, 704 and 755 days and received 54, 422, 493, 714, 1046 and 1132 mgm. of *number 29*. The first to die showed no tuberculosis, the second showed only slightly enlarged regional lymph nodes, the spleen, liver and lungs appearing normal. The next two showed marked generalized tuberculosis, while the last two, whose duration of life was in the neighborhood of two years, showed enlarged, hard fibrous lymph nodes, spleen slightly enlarged, but hard with fibrous scars, and liver and lungs dotted with a few small hard, necrotic scars. Two of this set had apparently advanced somewhat further toward healing than is common in guinea pigs.

(4) P-nitroso phenol O-mercuric chloride. The animals of this set lived 70, 90, 156, 247, 409 and 467 days and received 97, 131, 241, 381, 759 and 859 mgm. of the compound. The first three to die showed extensive generalization, the next showed no tuberculosis except in the regional lymph nodes which were enlarged but hard and fibrous, and the last to die showed considerable fibrosis of lymph nodes and tubercles in spleen, liver and lungs. Apparently there was more checking of progress and more healing at an earlier stage in this set than in the others I have described.

(5) *Number 20:* P-nitroso mercury diphenyl. This compound contains 48.2 per cent mercury and inhibits in dilutions up to 1 in 100,000. These animals lived 89, 91, 95, 420, 545 and 656 days and received 135, 137, 141, 535, 709 and 903 mgm. of the drug. Only the last two showed any evidence of fibrotic healing.

(6) Hirschfelder's nitrosaligenin or O-nitro phenol P-carbinol O-mercuric acetate. This compound prevented growth of tubercle bacilli in dilutions up to 1 in 100,000, but its tuberculocidal power was not great,

as not even 1 in 1000 showed any effect, even after exposure for twenty-four hours. The animals treated with this drug lived 95, 115, 280, 528, 552 and 680 days and received 121, 141, 306, 554, 578 and 706 mgm. All died of some infection other than tuberculosis and most had very little tuberculous involvement, although nearly all had at some time had enlarged tuberculous lymph nodes.

(7) *Number 15:* Na, 2, 2′ mercuri bis P-nitrophenol, caused complete inhibition of growth of human tubercle bacilli *in vitro* in dilutions up to 1 in 100,000. It had nearly complete tuberculocidal action at 1 in 1000 after twenty-four hours' exposure. The animals treated with this compound lived 42, 264, 526, 536 and 807 days, while one is still living at the time of writing after 816 days. They received 64, 452, 900, 910 and 1542 mgm. of the compound by mouth. All except one showed some generalized tuberculosis in lymph nodes, spleen, liver and lungs, though in most cases the involvement was slight. The two that lived the longest, two and a quarter years after inoculation, received a tuberculin test, May 1, 1923, the test being given on the eroded skin and also by injection into one testis. In both the test was negative. One of the guinea pigs which had been partially paralyzed and subject to convulsions during the last six weeks, died within fifteen hours after the tuberculin was administered. Many apparently entirely healed tubercles were found in enlarged lymph nodes, enlarged spleen, liver and lungs. Microscopic examination showed no caseation, completely fibrous tubercles, with a very few giant cells in one of the fibrous lymph nodes. This seemed one of the most evident cases of healing of well advanced tubercles in the guinea pig that has been noted in this laboratory. The other animal is still alive and would have been killed for pathological examination, except that it was being used for blood studies.

(8) *Number 14 M:* Mono-ethyl P-nitraniline O-mercuric acetate, causes complete inhibition of growth of tubercle bacilli *in vitro*, in dilutions up to 1 in 100,000, and complete tuberculocidal action in dilutions of 1 in 1000 and 1 in 10,000 after twenty-four hours' exposure. The animals treated with this compound lived 100, 346, 422 and 692 days and two are still living at date of writing, after 816 days. They received 118, 399, 529 and 992 mgm. of the compound, while the two that are still living have received 1560 mgm. The first two to die showed generalized and fairly extensive tuberculosis of lymph nodes, spleen, liver and lungs. The third showed only the lymph nodes involved. The fourth showed some enlarged, hard, fibrous lymph nodes, apparently partly or wholly

healed, with spleen slightly enlarged and liver fatty, while the lungs showed a moderate bronchopneumonia. The two that are still living gave a negative tuberculin test by both methods of administration, skin and testis, and would probably exhibit much the same pathologic picture as the one described under *15 Na.*

Weight Curves: A classification of weight curves of tuberculous guinea pigs, treated and untreated was worked out by me (6). The average gains and losses in weights of the different sets of guinea pigs in the chronic tuberculosis of *series 3* were charted in curves which may be compared with that general classification. It may be stated that the controls, the *number 15 Na* set and the number *14 M* set belong in *II C* of

TABLE 2

Table of average increases and decreases of weights of chronic treated tuberculosis

NAME OF SET	DURATION OF DISEASE	MAXIMUM HEIGHT OF CURVE	TERMINAL HEIGHT	DURATION OF ASCENT	DURATION OF DESCENT	WIDTH OF SUMMIT	TYPE OF CURVE
	weeks	*grams*	*grams*	*weeks*	*weeks*	*weeks*	
Controls	100	620	200	62	28	55	II C
No. 26. M-Nitro dimethyl aniline P-mercuric acetate	82	310	135	31	20	51	II E
No. 27. O-nitro dimethyl aniline P-mercuric acetate	86	375	−100	59	27	30	II E
No. 29. P-nitro monomethyl aniline O-mercuric acetate	98	610	20	51	48	40	II E
P-nitroso phenol O-mercuric chloride	65	770	410	59	6	28	II D
No. 20. P-nitroso mercury Diphenyl	88	1050	590	55	33	32	II D
O-nitro phenol P-carbinol P-mercuric acetate	98	400	−70	67	35	60	II E
No. 15 Na 2, 2′ mercuri bis P-nitro phenol	111	690	280	60	51	35	II C
No. 14 M Mono ethyl P-nitro aniline O-mercuric acetate	114	660	380	78	34	46	II C

that classification, that set *number 20* and P-nitroso phenol O-mercuric chloride belong in *II D*, and *number 26, 27, 29* and nitro saligenin are more comparable to *II E*, in that the height of the summit is lower and the elevation much wider than most of the other curves. These therefore give the effect of a very broad flat elevation, while *II D* has a slow ascent with a sharp apex and rapid descent, and *II C* has a slow ascent and descent forming a broad elevation with rounded summit. Table 2 itemizes the average weight findings used in charting these curves.

CONCLUSIONS AND DISCUSSION

While these experiments scarcely permit us to draw a definite favorable conclusion regarding the therapeutic value of organic mercurial compounds in experimental tuberculosis in guinea pigs, some of the findings seem to indicate that in a slowly progressive chronic tuberculosis certain of the compounds do bring about a definite fibrosis and healing of tubercles in different organs, such as is not found in any of the control animals, however long they live. One of the most favorable-appearing compounds is a nitrophenol derivative, numbered *15* in our list, and another is a nitraniline derivative known as *14 M* in our list. The small doses used and hence the small amount found distributed in the organs may explain the lack of more definite results in these experiments. These compounds, in the doses used, have produced no nephritis in any animal examined, beyond a slight distention of tubules near the capsule and an occasional fibrosis of some glomeruli.

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THE IODINE VALUE OF THE FAT CONTAINED IN LIVERS FROM TUBERCULOUS SUBJECTS[1]

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While working on fat metabolism Professor Aschoff asked me to determine the fat value and the iodine value of the fat contained in livers from tuberculous subjects. Now and then one comes across the highest grade of a fatty liver in a tuberculous subject, even though the body shows the gravest type of emaciation without a trace of adipose tissue anywhere else.

Before drawing any conclusions from the iodine value of fats of diseased organs, consideration must be given to the qualitative significance of fat in adipose tissue. This phase is well covered by the recent work of Beatson, Duncan and Currie. Beatson and Duncan carried out a systematic investigation of the iodine value of fats from subjects widely different in age and they found a constant iodine value of adipose-tissue fat, no matter from what portion of the body the fat was taken. Their figures are as follows:

1. For normal human fats in children under eleven the average iodine value was..... 44
2. Between the ages of 16 and 19 the iodine value was..... 60.88
3. Soon after puberty the iodine value was..... 61
4. Between the ages of 26 and 38 the iodine value was..... 62.1
5. Between the ages of 52 and 65 the iodine value was..... 63.98

The determination of the iodine value of fat from diseased organs has been the foundation of important arguments in pathology. The variable results obtained by earlier workers, like Kraus and Sommer, Rosenfeld, Leick and Winckler, and many others, are no doubt due to faulty methods of examination. Hartley was probably among the first whose results were reliable and who made a thorough study of the entire subject. He examined both diseased and normal organs. He showed that fats occurring in normal liver, kidney and heart differ

[1] From the Pathological Institute, University of Freiburg i/B., Germany, Professor L. Aschoff, Director.

in their properties from those found in the adipose connective tissue. The fat from the organs yielded on saponification a mixture of higher fatty acids, which is far more complex than the mixture obtained by saponification of the connective tissue fat. Thus the fatty acids from the adipose tissue have a low iodine value, according to age (44 to 65), while the fatty acids from normal organs have a very high iodine value (115 to 135). It is important to note that the fatty acids obtained from normal livers have a constant iodine value. The average amount of insoluble fatty acids to be obtained from normal human livers is about 12 to 17 per cent, calculated on the dry weight of the tissue.

The livers examined in this study were all from tuberculous subjects, the type of the disease and the grade of the fatty infiltration of the liver varying greatly, as can be judged from the table below. The microscopic pictures showed different stages of fatty infiltration; some showed marked infiltration only in the periphery of the liver lobule, others only in the centre, while in still others the entire parenchyma had been replaced by large fat globules. The nuclei in the majority of cases were well retained and did not show any degenerative changes. Eleven cases in all were examined. The numbers correspond to the autopsy numbers of 1922 at the Pathological Institute, University of Freiburg i/B., Germany.

Extracts from postmortem reports

162. Male, age 66. Caseous tuberculosis of both adrenals.

168. Female, age 36. Miliary tuberculosis of both lungs, spleen and peritoneum. Caseous tuberculosis of the retroperitoneal lymph nodes. Peripheral fatty infiltration of the liver.

171. Male, age 41. Chronic tuberculosis with cavity formation of both lungs. Chronic adhesive pleuritis. Irregular fatty infiltration of the liver.

195. Female, age 59. Chronic tuberculosis of both lungs with cavity formation. Chronic adhesive pleuritis. Congestion and fatty infiltration of liver. Marked fatty infiltraton of the adrenals.

223. Male, age 55. Chronic tuberculosis of both lungs with cavity formation. Chronic adhesive pleuritis. Tuberculous ulcerations in ascending colon and hepatic flexure. Tuberculous peritonitis. Very marked fatty infiltration of the liver.

225. Female, age 41. Chronic tuberculosis of both lungs with cavity formation. Tuberculous ulcerations of trachea and larynx. Tuberculous ulcers of ascending colon. Tuberculous endometritis and salpingitis. Very marked fatty infiltration of the liver.

226. Female, age 32. Miliary tuberculosis of lungs and peritoneum. Many tubercles in intima of pulmonary veins. Tuberculous ulcers of cecum. Fatty infiltration of the liver.

274. Male, age 2½. Miliary tuberculosis of lungs. Tuberculous meningitis.

283. Male, 16. Miliary tuberculosis of lungs, small and large intestines. Miliary tuberculosis of kidneys and thyroid. Fatty infiltration of the liver.

300. Male, age 74. Miliary tuberculosis of lungs, liver and kidneys.

NUMBER	CAUSE OF DEATH	FAT VALUE*	IODINE VALUE
162	Addison's disease	30	90.27
168	Miliary tuberculosis	60	67.38
171	Chronic tuberculosis	29.2	102.46
195	Chronic tuberculosis	27.3	110.5
223	Chronic tuberculosis, intestinal tuberculosis	65.8	72.4
225	Chronic tuberculosis, intestinal tuberculosis	72.4	64.3
226	Miliary tuberculosis	39.8	83.73
274	Tuberculous meningitis	26.2	69.2
283	Miliary tuberculosis	41.3	70.3
300	Miliary tuberculosis	47.2	80.2

* Fat value calculated on dry weight of tissue.

RESULTS

These examinations uphold the work of Hartley and Imrie. The higher the fat accumulation in the liver, the nearer its iodine value approaches the iodine value of adipose tissue fat. The law of Imrie states that when the amount of fatty acids of normal livers, fat infiltrated livers and adipose tissue and their iodine values are determined, the results show a relation to each other almost exactly as if the additional fat, over and above a certain amount normal for the liver, were all of it fat such as is found in adipose tissue. This law holds good for fat coming from livers of tuberculous subjects.

In these examinations the highest grade of fatty infiltration of the liver occurred in chronic tuberculosis associated with intestinal tuberculosis, as in cases 223 and 225. In case 274 the fat value is not high and, nevertheless, the iodine value is low. The subject was a child, two and a half years old, which explains the low iodine value, since the iodine value of adipose tissue in a child is about 44. This further tends to show that the fat in diseased livers comes from the adipose tissue fat.

CONCLUSION

The cause of fatty infiltration in the livers of tuberculous subjects is probably that of "fat retention." The fat is brought to the liver from the adipose tissue fat, but the liver is unable to utilize it and therefore accumulates it.

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STUDIES ON FUSIFORM BACILLI AND SPIROCHETES[1]

VI. THEIR ASSOCIATION WITH PULMONARY TUBERCULOSIS IN CAVITIES, BRONCHIECTASIS AND GANGRENE

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Fusiform bacilli and spirochetes have been noted as constantly present about the teeth. We have indicated their presence also in the tonsils and less often in the nasopharynx (1). Under certain conditions they become pathogenic agents in the lung, causing, frequently, abscess or gangrene. The normal lung apparently rarely becomes involved without other etiological factors. General anesthesia and aspiration of foreign bodies may lead to putrid pulmonary infection. The sputum in bronchiectasis frequently acquires a foul odor.

Although the tuberculous lung is very susceptible to many secondary infections, fusiform bacilli and spirochetes are concerned only rarely. When these secure a foothold in the tuberculous lung, abscess and gangrene may result. Buday (2), in his histological investigations of pulmonary gangrene, noted the occurrence of fusiform bacilli and spirochetes in one instance each of putrid bronchitis, gangrenous bronchopneumonia and diffuse gangrene in patients with pulmonary tuberculosis. In the earlier work on mixed infection in pulmonary tuberculosis by Kitasato (3), Cornet (4), Fränkel (5), Spengler (6), Schutz (7) and Ophüls (8), the anerobic microörganisms were not investigated. Similarly, in the later reports of Ravenel and Irwin (9), Flick, Brown, Pottenger and White (10), Hayes (11), Corper and Enright (12), fusiform bacilli and spirochetes were not included as secondary invaders. Veillon and Rapici (13) investigated the anerobic flora in foul sputum and cavities, and described *Micrococcus foetidus*, *B. funduliformis*, *B. ramosus*, *B. perfringens* and a small flagellated bacillus (*Spirillum crassum*).

In the following case reports are indicated the clinical and bacteriological findings in putrid infections associated with pulmonary tuberculosis.

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An example of marked fetid expectoration in a patient with far advanced pulmonary tuberculosis was the first type of infection noted.

Case 1: Female, colored, age 25, entered the hospital complaining of cough, foul expectoration and loss of weight. The onset dated five years previously, following apparently a normal puerperium. During childbirth she had had ether anesthesia. Cough, accompanied by loss of weight and strength, became progressively worse. The sputum was variable in amount, and did not become profuse and foul-smelling until a few months before entering the hospital. Physical examination revealed a greatly emaciated patient, temperature 102.6°F., pulse 120, respiration 30. The teeth were in good condition, except for heavy deposits of tartar; the tonsils were small and fibrous; the breath was extremely foul; the chest presented evidences of extensive involvement of all lobes, with typical signs of large cavitations in the left upper and right lower lobes. These findings were confirmed by fluoroscopic examination. The heart and abdomen presented no abnormalities. The urine was normal. The sputum was profuse, of green color and had an intense foul odor. Tubercle bacilli were found in abundance. In the washed sputum there were also enormous numbers of fusiform bacilli of various types together with slender and coarse spirochetes (fig. 1). The bacilli were often curved and short, like commas; others were long and granular. Diplococci and short chains of streptococci were intermingled with the other bacteria. Aerobic and anerobic cultures were made on 10 per cent blood agar. In the former *Streptococcus viridans* appeared, together with a few colonies of *Micrococcus catarrhalis;* in the latter a mixed culture of streptococci and pleomorphic forms of fusiform bacilli were obtained. In smears of the tartar of this patient enormous numbers of fusiform bacilli and spirochetes, identical with those seen in the sputum, were observed.

It is most probable that this patient had been ill with progressive ulcerative tuberculosis with cavity formation. Secondary infection with the fuso-spirochete organisms caused necrotic changes in the walls of the cavities with the production of a putrid exudate. A similar process was observed in bronchiectatic cavities associated with tuberculosis.

Case 2: Colored, male, age 13, entered the hospital, August 5, 1922, with a history of tonsillectomy under ether anesthesia in May, 1922, followed by pain in the chest, nights sweats and loss of weight and strength. The cough was frequent, with fetid sputum. The temperature fluctuated from 97° to 102°F., with rise usually in the afternoon. The pulse varied with the fever, from 100 to 140. Physical examination revealed moist râles in all lobes with

signs of cavitation in both upper lobes. Moderate hypertrophic arthropathy was evident in the extremities. Tubercle bacilli were not found in the sputum. The blood Wassermann reaction was negative. The sputum was very foul, forming three layers on standing. Direct smears of the washed portion of the bottom green layer revealed typical straight and curved forms of fusiform bacilli, short comma bacilli and short and long spirochetes, together with diplococci and short and long chains of streptococci. Aerobic cultures on blood agar gave predominantly *Streptococcus viridans*, a few colonies of *Staphylococcus albus* and gram-positive diphtheroids. Anerobic slants were foul-smelling, containing cocci and pleomorphic forms of fusiform bacilli.

The patient became progressively worse and died December 9, 1922. At autopsy the left lung presented numerous fibrinous and fibrous adhesions. Stinking pus exuded from the trachea and bronchi. Diminished crepitus occurred throughout. On section there were numerous cavities, many of which were bronchiectatic and filled with foul green pus. In the walls, immediately surrounding the cavities, were numerous miliary tubercles. The right pleural cavity was filled with thick foul pus. The pleural cavity communicated with an abscess cavity, in the lower lobe, which contained 40 cc. of fetid pus. The cut section showed thickened bronchi, opening into numerous small bronchiectatic cavities in both upper and lower lobes; several larger cavities were distinctly removed from the bronchi. The walls of the cavities were necrotic, of grayish-green color. Tubercles were scattered throughout the lung. One tracheobronchial lymph node was enlarged and caseous. The others were also large and soft. Smears made from the necrotic areas of the abscess wall revealed fusiform bacilli, spirochetes and cocci similar to those described in the sputum. In the liver moderate fatty changes occurred. Submucous hemorrhages were found in the stomach and intestines.

In histological sections of the lungs complicated pathological changes were evident. The tubercles were disseminated and often caseous. Distinct nontuberculous bronchopneumonic areas with necrotic centres coexisted. The softened areas contained gram-positive cocci and fusiform bacilli, the cocci extending out into the less necrotic tissue. In Levaditi preparations spirochetes were present in the necrotic areas and in the walls of the bronchiectatic cavities. The dilated bronchi were filled with leucocytes and masses of bacteria. The final diagnosis was multiple putrid bronchiectatic cavities of both lungs; multiple putrid abscesses of right lung; right-sided putrid empyema; miliary tuberculosis of all lobes; caseous tuberculosis of the peribronchial lymph glands.

It would seem most probable that the pulmonary condition was primarily a bronchiectasis, following tonsillectomy, and complicated by infection with fusiform bacilli and spirochetes; subsequently, extension of

the infection by the same bacteria caused multiple abscesses, one of which ruptured into the right pleural cavity causing the empyema; miliary tuberculosis occurred late, originating possibly from the caseous peribronchial lymph node.

Case 3: White, male, age 45, Polish laborer, complained of cough, profuse expectoration, progressive weakness and loss of weight. The cough was chronic for three years. Blood was noted in the sputum six months prior to entrance, with an increase in the amount of expectoration. The fetid odor was noticed at various intervals. While under observation the temperature in the afternoon rose to 103° and 104°, and the pulse varied from 120 to 140. Physical examination revealed an emaciated adult. The teeth were very poor and carious, with moderate pyorrhea and heavy tartar deposits. The breath was foul. In the chest impaired resonance occurred in both upper lobes, with moist râles in the left upper and the entire right lung. Roentgen plates revealed mottling of the upper lobes, with small scattered cavities throughout the right lung. The leucocyte count was 8,600; erythrocytes 4,160,000; hemoglobin 70 per cent. The blood Wassermann was negative and the urine normal. The sputum was large in amount, measuring from 10 to 16 ounces daily, forming three layers, a bottom grayish-green, middle clear watery and an upper frothy. The odor was foul. Smears were made of all three layers and straight and curved forms of fusiform bacilli spirochetes and cocci occurred in large numbers in all layers. Tubercle bacilli were present in moderate numbers. Aerobic cultures on blood agar gave streptococcus viridans and staphylococcus albus. In anerobic cultures the same cocci were found together with fusiform bacilli.

Case 4: D. P., male, age 34, white, gave history of cough and foul expectoration for two years following an attack of "acute bronchitis and pleurisy." Physical and roentgen examination indicated dense infiltration of the right apex and left upper lobe to the fifth rib posteriorly. On examination, eight months later, the infiltration extended to the level of the seventh rib, with small cavity formation. Tubercle bacilli were present in the sputum. The urine and blood Wassermann reaction were negative. The sputum formed three layers. In the washed bottom layer large numbers of fusiform bacilli, spirochetes, gram-positive lancet-shaped diplococci and short chains of streptococci were found. No cultures were made.

In these patients the condition was probably at the beginning tuberculous, with secondary infection with the anerobes and cocci, to form simple or bronchiectatic abscesses.

Of special interest because of its rarity and striking picture is the occurrence of gangrene in a tuberculous lung as illustrated in the following patient.

Case 5: F. M., white 38, male, clerk, entered the hospital complaining of cough, weakness and loss of weight beginning two months previously. The cough was frequent, accompanied by pain in the right axilla and expectoration of moderate quantities of foul sputum. The patient had been an excessive consumer of alcohol. The afternoon temperature was 101°F. to 103°F., pulse 100 to 120 and respiration 22 to 24. Examination revealed a well-developed and well-nourished adult, weighing 150 pounds. The breath was foul. The teeth were absent, as he had a false set. The tonsils were atrophic. Dulness was present over the entire right lung, with impaired resonance of the left upper lobe. The fingers were clubbed. The systolic blood pressure was 94 and diastolic 66; the leucocyte count was 11,900; the urine contained a trace of albumen. The sputum was very foul, liquid and green. Tubercle bacilli were found in moderate numbers. Smears revealed many short, straight, curved and long filamentous forms of fusiform bacilli. Some of the bacilli were quite large and granular, with sharp or blunt ends. A few short slender and long coarse spirochetes were found, after long search of several specimens. Many diplococci were constantly present. Neosalvarsan (0.9 gm.) was administered intravenously without improvement, and death occurred one week later. At autopsy the body appeared well-nourished. The left pleural cavity was obliterated by fibrous adhesions, the right partially by similar adhesions over the upper lobe. The trachea and bronchi were intensely hyperemic. The peribronchial lymph nodes were enlarged and soft, and on section anthracotic and fibrous. The right lung presented sunken areas in the upper lobe. The pleura was covered by fibrous and fibrinous adhesions, the fibrin being deposited in scattered patches on the upper lobe. Crepitus was decreased in the upper lobe and there were many solid areas in the lower lobe. The cut section was very putrid, with extensive softening and green color in the upper lobe. Four cavities, from 3 to 6 cm. in diameter, occupied a large part of the upper lobe and were filled with green, foul, necrotic material. Beyond the necrotic tissue of the cavity wall were areas made up of fibrous tissue and caseating nodules. In the lower lobe were raised, firm, confluent nodules, often with caseous areas. The middle lobe was emphysematous and edematous; the weight was 900 grams. The left lung was filled with fluid; the pleura was covered with fibrous tags; the upper lobe was nodular in its middle portion. The cut section revealed raised areas that were firm and made up of fibrous tissue and caseating areas, together with small cavities, 1 to 2 cm. in diameter. The weight was 800 grams. The anatomic diagnosis was diffuse gangrene of the right upper lobe; chronic

fibrocaseous tuberculosis of the right upper and lower and left upper lobes; cloudy swelling of the liver, spleen, kidneys and myocardium; petechial hemorrhages of the stomach and intestines.

Smears made from the gangrenous areas of the lung revealed the various types of fusiform bacilli found in the sputum, diplococci and strikingly large numbers of spirochetes. In aerobic cultures appeared many colonies of *Streptococcus hemolyticus* of the beta type, and a few *Staphylococcus albus* and *aureus*. In the anerobic cultures similar cocci with pleomorphic forms of fusiform bacilli were present. To determine the pathogenicity of the bacteria found, rabbits were injected with macerated lung from the gangrenous portion. The material was suspended in salt solution and 1 cc. injected into the pleural cavity. The rabbit became very ill and was killed six days after injection. A markedly putrid exudate, green in color, filled the cavity; fusiform bacilli, spirochetes and cocci were demonstrated in abundance. A second rabbit was injected with 0.5 cc. of the same material into the testes. Abscess formations with rapid necrosis and sloughing resulted, with death of the rabbit on the fifth day. From the sloughing lesion many fusiform bacilli and cocci but no spirochetes were demonstrated.

In histological sections made of the lungs, there appeared a mixed picture of tuberculosis and gangrene in the right lung and tuberculosis in the left. The right apex presented a thickened pleura, with coal pigment immediately underneath. The connective tissue was increased in all sections. The alveoli were densely infiltrated with round cells forming confluent areas of bronchopneumonia. Many of the consolidated areas were necrotic in the centre (fig. 2). The walls of the cavities were made up of poorly staining necrotic tissue, adjacent to which the lung parenchyma was densely infiltrated with polymorphonuclear leucocytes. In both lobes of the right lung were seen areas of caseation and fibrosis, representing the remnants of the tuberculosis. Sections of the opposite lung revealed confluent areas of consolidation, with considerable fibrosis and caseation. From this region tubercle bacilli were demonstrated in large numbers.

Different portions of the gangrenous lung were stained by the Levaditi method. At the wall of the cavities only a few spirochetes were intermingled with large numbers of fusiform bacilli and cocci (fig. 3). Immediately adjacent to the wall in less necrotic areas the spirochetes were in great numbers, while the bacilli and cocci were fewer. As one studied the tissue farther from the necrotic areas the spirochetes became more numerous and predominant, with only an occasional diplococcus (fig. 4). Such a distribution of microörganisms was quite constant in several different parts of the lung, so that it would seem that spirochetes invaded the tissue in advance of the bacilli.

Several points of interest are noteworthy in the last patient. The gangrene was unilateral in an individual with bilateral fibrocaseous tuberculosis. The tuberculosis was not disabling, for the patient was in

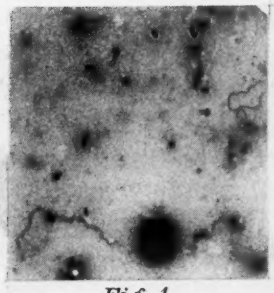

Fig. 1

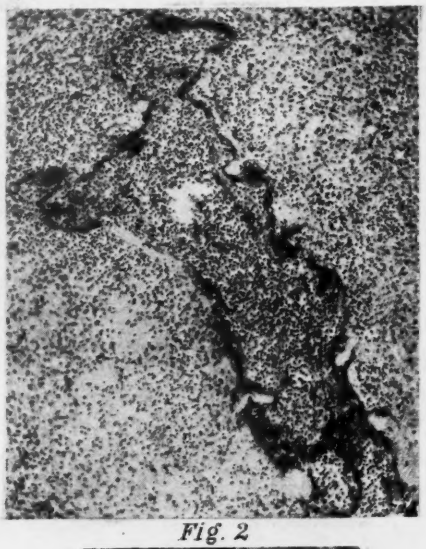

Fig. 2

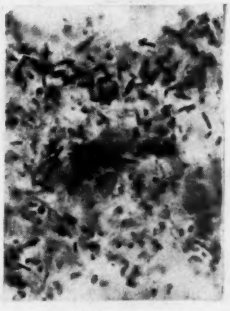

Fig. 3

Fig. 4

FIG. 1. FUSIFORM BACILLI, SPIROCHETES AND COCCI IN SPUTUM

Case 1. Stained with carbol fuchsin

FIG. 2. AREA OF GANGRENE IN LUNG

Margin is made up of advancing zone of bacteria. Case 5. Eosinhematoxylin stain

FIG. 3. MASS OF MANY FUSIFORM BACILLI, COCCI AND FEW SPIROCHETES AT LINING OF ABSCESS CAVITY

Case 5. Levaditi stain

FIG. 4. SPIROCHETES IN FIBROUS TISSUE IN LUNG WITH FIBROID PHTHISIS AWAY FROM ABSCESS WALL ILLUSTRATED IN FIG. 3

Levaditi stain

comparatively good condition until gangrene was superimposed and carried him away in a few weeks. In the diagnosis, although the sputum was very fetid, only a few spirochetes were found. At autopsy, the spirochetes occurred in enormous numbers in the lung but were found chiefly away from the necrotic walls of the cavities. The fusiform bacilli and cocci, which were abundant in the sputum, were found to make up the bacterial masses that lined the cavity wall. This finding would indicate that the absence of spirochetes in sputum does not exclude their presence in the lung tissues. Indeed, if the fusiform bacillus is seen in the sputum one can reasonably assume that the symbiotic spirochetes are associated with them in the pulmonary lesion. Neosalvarsan was employed because of its spirocheticidal properties, but the gangrene was so far advanced that no deductions can properly be made as to the therapeutic action of arsenic. Lastly, putrid lesions were produced experimentally in rabbits by injecting small quantities of the macerated gangrenous lung.

Putrid infections, as illustrated by the foregoing cases, may complicate various forms of tuberculosis, such as the advanced ulcerative with large cavity formation, in which there may be an associated putrid bronchitis or gangrene in the cavity wall; tuberculous bronchiectatic cavities, with or without abscess formation; and the chronic fibrocaseous type with abscess or gangrene. In the production of these infections the fusiform bacillus and the associated spirochetes, together with pyogenic bacteria, usually streptococci, are largely responsible. We have, however, observed secondary infection with *B. pyocyaneus*, with the production of extremely foul-smelling sputum. The occurrence of the fuso-spirochete infection in various forms of tuberculosis suggests that the sources of infection may be the same in most instances and may be traced to the habitat of these microörganisms in the mouth and pharynx.

The tartar of the teeth has been long recognized as harboring large numbers of fusiform bacilli, spirochetes and cocci. In cases 1 and 3 the tartar deposits were heavy, and the microörganisms were found in large numbers in smears made from the gums and tonsillar surfaces. In case 5 the patient carried teeth plates, about which heavy deposits of tartar tend to accumulate. Other common habitats are the faucial tonsils and the nasopharynx. Fusiform bacilli, often with spirochetes, are found in the tonsils of 82 per cent of persons, and in 32 per cent in adenoids. In tonsillar crypts they frequently form firm, yellow,

foul-smelling masses. In both teeth and tonsils *Streptococcus viridans* and often *Streptococcus hemolyticus* are found in association.

Certain factors determine fuso-spirochete infection of the lung. Under general anesthesia aspiration of mouth secretions, especially during tonsillectomy, may lead to abscess or gangrene. Foreign bodies may carry the infection into nontuberculous lungs. Apparently, the tuberculous lung itself is predisposed to secondary infection, with or without the factors of aspiration. More commonly, such infections arise from the ordinary pyogenic microörganisms about the mouth, as streptococci, pneumococci, *B. influenzae* and staphylococci. Rarely, infection results from the fusiform bacilli and spirochetes. Pure fuso-spirochete infection does not occur but is combined with streptococci or other pyogens.

One of the striking clinical signs of fuso-spirochete infection is the foul breath and sputum. Foul breath, due to infections of gums, teeth and tonsils, should be excluded before pulmonary involvement is suspected. The sputum varies in appearance and amount. In bronchiectasis and abscess the quantity is large, forming three layers. In gangrene the sputum is thin and green, and may contain necrotic lung tissue. Elastic tissue is not constant. The odor is important, for we have observed fusiform baccilli and spirochetes in sputum with no odor, in patients who harbor these microörganisms as saprophytes in the bronchi as in the mouth. When the sputum becomes foul the odor is due to the growth of the microörganisms in the tissues, with the production of a lesion.

Microscopic examination of the sputum reveals detritus, made up of pus cells, desquamated epithelium and mucus. The microörganisms occur in large clumps. In making smears it is important to select proper portions of the sputum and to avoid mouth secretions. Washing the sputum repeatedly with physiological salt solution can eliminate the microörganisms of the saliva. The smear is made slowly, without spreading the material too vigorously, as the spirochetes are easily distorted. Carbol fuchsin (10 per cent) or the Fontana stain can be employed. The fusiform bacilli appear as short or long forms, with pointed or slightly blunt ends. They may be solid, granular or barred. Frequently the short forms are curved, the smallest resembling commas. The bacilli are weakly Gram-positive. The spirochetes vary in morphology, appearing as short slender forms, with 3 to 5 undulations, or longer and coarser with 5 to 15 turns. Usually several types occur in

the same smear. In morphology they are identical with those seen about the teeth and tonsils and in Vincent's angina. Intermingled with these microörganisms are invariably cocci, especially streptococci. Pneumococci, staphylococci and *Micrococcus catarrhalis* are occasionally encountered.

In cultures the fusiform bacilli can be grown on blood agar, under anerobic conditions, and appear in pleomorphic forms. The spirochetes fail to grow; the cocci are usually streptococci, either green or hemolytic or both. In their morphology, cultural characteristics and fermentation properties these streptococci resemble those isolated from tonsils and teeth.

In the tuberculous patient proper care and hygiene of the mouth should lessen the dangers of infection with these microörganisms. Heavy tartar deposits should be removed and infected gums and carious teeth treated. If, in the tonsils there is a tendency to the accumulation of masses of bacteria, expression may be employed. Of special importance is thorough hygiene and preparation of the mouth in patients requiring operative procedures about the throat and general anesthesia.

In recognized fuso-spirochete infections of the lung arsphenamine and neoarsphenamine deserve a trial. We have not studied their effect in abscess and gangrene in the tuberculous but we have obtained striking results in several nontuberculous patients with bronchiectasis, abscess and gangrene.

SUMMARY

Fusiform bacilli and spirochetes cause secondary infection in pulmonary tuberculosis. They are usually responsible for the fetid expectoration in bronchiectasis and gangrene.

Pyogenic bacteria, usually *Streptococcus viridans* or *hemolyticus*, are associated with the fuso-spirochetes in the sputum and the lungs.

The sources of infection centre about the teeth, tonsils and nasopharynx which harbor these microörganisms normally.

Prevention of these putrid infections depends on proper care and hygiene of the mouth.

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THE PRESENCE OF VIRULENT TUBERCLE BACILLI IN HUMAN BILE[1]

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Recently Freed and Black (1) in our laboratories found that, in questionable or doubtful cases of pulmonary tuberculosis, in which routine sputum smears failed persistently to reveal tubercle bacilli, the bile, obtained by means of the duodenal tube and a duodenal douche of magnesium sulphate solution (Meltzer and Lyon), was capable of infecting guinea pigs in 2 of 12 cases, the sputum, gastric and duodenal contents being negative. They recommended that guinea pig inoculation be resorted to in sputum-negative cases, using sputum and gastric and duodenal contents besides the bile obtained by means of the duodenal douche. In the case of 7 children of an orphanage, exposed to two fatal cases of severe pulmonary tuberculosis, tubercle bacilli were found in the bile of one of the contacts by this method. They warn that when the possibility of milk contamination exists this should be guarded against by determining the strain of bacillus found.

That tubercle bacilli occur in the bile of tuberculous animals is not to be doubted, although data as to the time of their appearance in the bile, in relation to the stage of disease, are lacking. The presence of bacilli in the bile is usually accounted for by their being deposited in the liver from the blood stream, and from there passing into the bile, to be excreted into the intestines. Although it has not been definitely proved experimentally that bacilli from foci in the lungs are eliminated by way of the liver, this transport is expressed as likely by Calmette, and independently by Rabinowitsch, and there seems to be just as much reason for the possibility as against it. Certain facts seem to speak in favor of this view although direct evidence in man is lacking; for instance, the finding of tubercle bacilli in the circulating blood in a small though definite number of cases of pulmonary tuberculosis, as well as the develop-

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ment of metastatic foci in certain pulmonary cases in man. Recent interesting contributions by Drinker and his colleagues (2) indicate that particulate matter injected intravenously lodges mainly in the lungs, liver, and spleen, and that shortly afterwards much of the material primarily lodged in the lungs in cats has been transferred to the liver. They believe also that they have demonstrated, without doubt, that particles of manganese dioxide pass through the liver into the bile of rabbits. However, manganese metasilicate, a less soluble salt of manganese, does not shift from the lungs to the liver; and it may be that the manganese dioxide is transferred in soluble form, a question they leave open and for future solution. However, this much is clear from their work: that particulate matter entering the circulation passes to the liver from which it may be excreted in the bile.

Remlinger (3) examined the bile of 24 guinea pigs dead of tuberculosis, by inoculation into normal guinea pigs, and found that it was capable of infecting 18 of the 24 test animals. The total bile removed from the gall bladder was injected into the test guinea pig. The total urine taken from the bladder of 24 tuberculous guinea pigs produced tuberculosis in 12 of the 24 test animals. Calmette and Guerin (4) found tubercle bacilli in the bile of rabbits that had received the bacilli by inoculation into the marginal ear veins. From biliary fistulae in 2 calves that had been infected by inoculating human and bovine tubercle bacilli into the jugular vein, Calmette was able to draw off bile at different periods which infected guinea pigs (15 of 109 in one experiment and likewise 3 of 66 guinea pigs after the inoculation of human bacilli). There are numerous other reports of the finding of tubercle bacilli in the bile of animals postmortem (among tuberculous cattle or pigs the findings reported are 16 to 42 per cent positive inoculation findings); but, in so far as human beings are concerned, the literature is scanty if reliable guinea pig inoculations are considered. There are some reports in which stained microscopic preparations were examined but, when one realizes the possibility of error by this method, as was well pointed out during the controversy about a decade ago on the presence of tubercle bacilli in the blood, these findings are to be accepted with a great deal of scepticism and are open to severe criticism.

So far as we were able to find, there were only two reports on the subject of the presence of tubercle bacilli in human bile directly examined by guinea pig inoculation. In 1899 Fraenkel and Krause (5), by animal inoculation, found tubercle bacilli in the bile of 5 of 11 cases (45 per cent)

of tuberculosis examined postmortem. In 1913 Lydia Rabinowitsch (6) examined the bile, postmortem, in 17 cases, 16 of which had more or less advanced tuberculosis, while one case only had calcified mesenteric lymph nodes. In 11 of the cases the intestines were macroscopically involved, and in two the liver was involved. Inoculation of guinea pigs resulted positively in 12 cases (70 per cent). Microscopic examination of antiformin-prepared specimens proved inadequate (3 only being positive). Among the twelve positive cases, intestinal changes were found eight times. She attributed her high percentage of positive findings to the fact that her cases were advanced and that the guinea pigs were inoculated both subcutaneously and intraperitoneally. In the majority of the cases the liver revealed no tuberculous involvement. Attempts to cultivate the bacilli from the bile were also uniformly negative.

The following observations were made, in order to elaborate upon the study initiated by Rabinowitsch on human postmortem biles, and to serve as a further foundation for diagnostic measures by the duodenal douche method for finding tubercle bacilli in the bile, as reported by Freed and Black. All the biles were obtained from human cases, postmortem, from the National Jewish Hospital for Consumptives or the Fitzsimmons General Hospital of Denver, Colorado. The technique, in brief, consisted of searing a wide area on the surface of the gall bladder and withdrawing from it, by means of a sterile glass pipette, from 5 to 10 cc. of bile. All biles were obtained within six hours of death and were then kept in sterile flasks in perfect darkness until they were prepared for guinea pig inoculation, this period not exceeding four to six hours after withdrawal of the bile. The bile was mixed with an equal volume of 4 per cent sodium hydroxide and kept at 37°C., being frequently shaken for about 20 to 30 minutes, after which the material was diluted with sterile 0.9 per cent sodium chloride solution, centrifugated, and the sediment washed twice with sterile salt solution. The washed sediment was then shaken up in a small amount of sterile salt solution and injected subcutaneously into guinea pigs, 2 to 3 animals being used for each specimen of bile examined. The animals were then examined carefully two to three months after inoculation for the presence of tuberculosis. Bile from 25 postmortem cases was inoculated into guinea pigs with the following summarized results:

In 4 of 18 uncomplicated far advanced cases of tuberculosis the inoculation of the bile resulted in generalized tuberculosis in guinea pigs within two months afterward. Anatomically, the 4 cases were pulmonary cavity cases; in one the tuberculosis was limited mainly to the lungs, while the remaining 3 were more or less general in distribution, with ulcerative enteritis and enlarged thoracic and abdominal lymph nodes, only one of the latter, however, terminating as a generalized miliary tuberculosis. Of the 25 cases examined, the biles from two more, besides the above four, were also positive by guinea pig inoculation, one a moderately advanced case of definite tuberculosis and one a case of tuberculosis in which death was due directly to an aortic aneurysm. Among the cases in which the bile was negative were one case of incipient tuberculosis, one of gangrene of the lung (superimposed on tuberculosis), 2 of streptococcus pneumonia and pulmonary abscess, and one of lumbar caries and psoas abscess.

DISCUSSION

The finding of tubercle bacilli by guinea pig inoculation in the bile of 6 of 25 cases of tuberculosis examined, only 23 of which could be considered as originating from clear-cut cases of pulmonary tuberculosis, seems to justify the use of the Meltzer-Lyon duodenal douche diagnostic procedure, suggested by Freed and Black in sputum-negative and suspected cases of pulmonary tuberculosis for the determination of tubercle bacilli in the bile, as well as in the gastric and duodenal contents.

The positive postmortem bile findings recorded in this study are lower than those reported by Rabinowitsch or by Fraenkel and Krause; but this difference may be accounted for by the variation in the material used and possibly also by slight differences in the technique, yet the significant point in the three studies is the unquestionable positive findings. It is true that most of the positive findings are recorded in advanced cases of tuberculosis; but may we not infer that findings which occur frequently at death may be sufficiently frequent in the earlier stages of the disease to be of value? At least this would seem justified from both direct and indirect available evidence.

That particulate matter entering the circulation may ultimately enter the liver, and then be excreted by way of the bile, is indicated by a number of studies, including those by Drinker and his co-workers

with insoluble manganese compounds and those by Calmette and his colleagues with tubercle bacilli. There is, however, still doubt as to whether particulate matter or tubercle bacilli, harbored in the lungs, may find their way into the circulation, be carried to the liver and finally be excreted in the bile. This opinion is held by many observers, but it lacks the indisputable stamp of final and detailed analysis. It is surely highly probable, especially in the case of tuberculosis in which caseation of a tubercle occurs, with ulceration and rupture of the caseous material into a blood vessel. Just how often this may happen, can, however, only be conjectured. A strong argument in favor of this view in tuberculosis has always been the occasional development of distant metastatic tuberculous foci such as are found in the bones, kidneys, central nervous system and various other parts of the body; another argument seems to be the finding of tubercle bacilli in the blood, especially the increasing incidence with advance of the disease. No doubt, if this does occur, and it seems highly probable from the evidence at hand that embolic showers of caseous material containing bacilli may occur irregularly and at indefinite periods, it might account for the absence of the bacilli in the bile, even in the advanced cases; yet when tubercle bacilli are found with certainty, especially by animal inoculation, it stands as indisputable evidence of the presence of tuberculosis provided, of course, contamination from external sources is excluded. Therefore, from the scientific and experimental evidence at present available it seems desirable in suspected cases of tuberculosis to examine the bile by animal inoculation for the presence of tubercle bacilli. It remains for future and more elaborate studies to determine in what cases of tuberculosis and how frequently tubercle bacilli occur in the bile.

SUMMARY

1. Tubercle bacilli were found in the bile postmortem, by guinea pig inoculation, in 4 of 18 cases of far advanced ulcerative pulmonary tuberculosis, in 1 case of moderately advanced pulmonary tuberculosis and in 1 case of advanced tuberculosis complicated by aortic aneurysm.

2. The biles, postmortem, from 1 case of incipient tuberculosis, 1 of pulmonary gangrene, 2 of streptococcus pneumonia and pulmonary abscess, and 1 of lumbar caries with psoas abscess, were negative.

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THE WIDAL TEST IN TUBERCULOSIS[1]

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A positive Widal test is ordinarily considered an indication of typhoid fever, provided the disease has progressed sufficiently for the production of agglutinins. In using the microscopic Widal test with dried blood specimens submitted on parchment paper, we have obtained positive tests in patients without typhoid fever. In two instances recently in our laboratories such false positive tests have been reported for patients who later were diagnosed as having tuberculosis and not typhoid fever.

A search of the literature reveals almost nothing on this subject. Wood (1), in his text book a number of years ago, pictured a true agglutination reaction from a case of typhoid fever, along with a false partial reaction in tuberculosis. Conversations with other laboratory workers indicate that this phenomenon has at times been noted but not studied. Porter (2), in making a large number of Widal tests, differentiated between a true agglutination in typhoid fever and a partial agglutination in tuberculosis. In every instance where information was available a focus of tuberculosis was found in patients giving the latter reaction. At his suggestion the following study was undertaken.

Method of study: Daily there are submitted to our laboratories a large number of blood specimens for the tuberculosis-fixation test. These specimens were tested against a twenty-four-hour live culture of *Bacillus typhosus*, grown on slant agar at room temperature and washed off with physiological sodium chloride solution. For accurate dilution the clear serum was diluted 1 to 20 and a drop of this mixed with a drop of culture suspension, making a 1 to 40 final dilution. The hanging-drop preparations were sealed with vaseline and incubated one hour at 37°C. Histories of the patients from which the specimens came were obtained, as far as possible, from the attending physicians.

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WIDAL TEST AND TUBERCULOSIS-FIXATION TEST

One hundred specimens were tested by both Widal and tuberculosis-fixation tests. There was no close agreement of the two tests, as is indicated in table 1.

In this table partial reactions have been listed with the strongly positive. It will be noted that there was agreement in 62 per cent of the two tests and disagreement in 38 per cent. Tables 2, 3 and 4 show the figures in detail.

WIDAL TEST AND TUBERCULOSIS

In response to a questionnaire, forty physicians returned histories of the patients, 7 of which were diagnosed definitely as tuberculosis, 17 definitely as with no symptoms of tuberculosis and 26 as doubtful or suspicious.

In tables 2, 3 and 4 are given the figures obtained in detail. Nine cases of typhoid fever are reported, ranging from the present time to sixty years ago. In only three instances, however, was the Widal test rendered positive by typhoid fever. In two instances typhoid vaccination was reported, one, however, being in 1906, which is apparently an error.

TABLE 1

Widal and tuberculosis-fixation tests

	POSITIVE TUBERCULOSIS FIXATION	NEGATIVE TUBERCULOSIS FIXATION	TOTAL
Positive Widal	25	28	53
Negative Widal	10	37	47
Total	35	65	

In regard to the diagnosis of tuberculosis, probably many of the cases in the doubtful list of table 3 should come in the positive list of table 2. Fifteen had at some time shown symptoms of tuberculosis, and apparently there was some suspicion at the present time of the disease, since a tuberculosis-fixation test was requested. The same could be said of the negative list in table 4.

The Widal test seems to be positive in the incipient and beginning cases of tuberculosis, and negative in the far advanced cases. Twelve specimens of blood were received from patients in a tuberculosis sanatorium, the cases all being advanced tuberculosis. These specimens were taken

on parchment paper, allowed to dry, and diluted with distilled water, the dilution being estimated by the color of the hemolyzed cells. In no instance was the microscopic Widal test positive. In this connection, however, another case should be cited, of which a blood specimen was

TABLE 2

History of patients definitely diagnosed tuberculosis

	TUBERCULOSIS FIXATION	TYPHOID HISTORY	TYPHOID VACCINATION	WIDAL TEST	TUBERCULOSIS SYMPTOMS
1	ac	1913	1920	+	0
2	0	0	0	0	1922
3	+	0	0	+	1922
4	0	0	0	0	0
5	+	0	0	+	1922
6	+	0	0	0	?
7	+	0	0	+	1922

TABLE 3

History of patients with doubtful tuberculosis symptoms

	TUBERCULOSIS FIXATION	TYPHOID HISTORY	TYPHOID VACCINATION	WIDAL TEST	TUBERCULOSIS SYMPTOMS
1	0	0	No	0	1922
2	0	Present time	No	+	0
3	+	0	1906	±	1919
4	−	0	0	+	Malaria 1915
5	+	0	0	+	1922
6	0	1876	0	0	0
7	0	0	0	±	1921
8	0	1919	0	0	18 years ago
9	+	0	0	0	1922
10	0	0	0	+	15 years ago
11	+	0	0	0	4 years ago
12	ac	0	0	0	1922
13	+	0	0	+	0
14	0	1909	0	0	1919
15	+	−	0	+	0
16	0	0	0	±	10 years ago
17	ac	0	0	+	0
18	0	−	−	±	0
19	ac	0	0	+	1918
20	ac	0	0	0	0
21	±	0	0	+	0
22	0	1908	0	0	0
23	ac	0	0	0	0
24	±	0	0	0	1922
25	±	0	0	±	3 years ago
26	+	0	0	0	1914

submitted on parchment paper from a woman in one of the state institutions. This was a routine Widal specimen and was tested with no knowledge of the condition of the patient. The Widal test was positive. The institution reported to us that the woman died the next day of advanced tuberculosis and with no evidence of typhoid fever. It would seem, therefore, that sometimes advanced cases of tuberculosis may give positive Widal tests.

TABLE 4

History of patients with negative tuberculosis symptoms

	TUBERCULOSIS FIXATION	TYPHOID HISTORY	TYPHOID VACCINATION	WIDAL TEST	TUBERCULOSIS SYMPTOMS
1	0	0	0	±	0
2	0	1902	0	0	0
3	0	1863	0	0	0
4	0	0	0	+	0
5	+	0	0	+	0
6	+	0	0	+	0
7	0	0	0	0	0
8	0	0	0	+	0
9	0	0	0	0	0
10	+	0	0	+	0
11	+	1911	0	±	0
12	0	0	0	0	0
13	0	0	0	0	0
14	0	0	0	0	0
15	+	0	0	±	0
16	+	0	0	+	0

EFFECT OF DRYING THE BLOOD

Although dried blood specimens had been used in the routine Widal tests for the diagnosis of typhoid fever, with a positive reaction now and then in tuberculosis, for these experiments fresh serum from the blood tubes was diluted as described previously. To determine whether drying of the blood had any effect on the results obtained, several of the blood specimens from the tuberculosis-fixation tests, which had given positive Widal tests, were smeared on parchment paper and allowed to dry. The next day these were tested in the usual manner by diluting with distilled water and estimating the dilution by the color of the hemolyzed cells. In each instance the reactions were identical with those obtained with the same fresh blood specimen.

AGGLUTINATION OF OTHER MICROÖRGANISMS

Various members of the colon-typhoid group were tested with four serums from patients which had previously given positive Widal tests.

It will be noted in table 5 that *B. dysenteriae Flexner* gave much stronger reactions than *B. typhosus* and that none of the other bacteria gave any reactions aside from a doubtful instance with one strain of *B. coli.* Further tests were set up using the typhoid bacillus and the Flexner bacillus side by side. In nine instances the results checked, in two instances the typhoid bacillus was agglutinated while the dysentery was not and in three instances the reverse was true.

TABLE 5

Agglutination of colon-typhoid group by tuberculosis serums

	SERUM 1	SERUM 2	SERUM 3	SERUM 4	CONTROL
B. typhosus	±	±	0	+	0
B. paratyphosus A	0	0	0	0	0
B. paratyphosus B	0	0	0	0	0
B. dysenteriae Shiga	0	0	0	0	0
B. dysenteriae Flexner	±	++	++	++	0
B. dysenteriae Hiss	0	0	0	0	0
B. coli 51	0	0	0	0	0
B. coli 52	0	±	0	0	0

MACROSCOPIC AGGLUTINATION

Twelve specimens were tested by the macroscopic agglutination method, using a dilution of the serum of 1 to 40. After incubation at 56° C. for one hour, the tubes were placed in the icebox overnight and read the next morning. While eight specimens were positive by the microscopic method both with typhoid and Flexner bacilli, the macroscopic tests gave negative reactions. In several instances there was a precipitate in the tubes, but this was easily distinguishable from true agglutination.

SUMMARY AND CONCLUSIONS

The microscopic Widal test has been found to give positive reactions with many cases of tuberculosis in which there was no history of typhoid fever. The tuberculosis-fixation test and the microscopic Widal test corresponded in 62 per cent of the cases. In checking up the histories of the patients, as far as possible, from the attending physicians, out of

40 individuals 7 were diagnosed definitely as with tuberculosis, 4 of which gave positive Widal tests; 26 were diagnosed as doubtful or suspicious for tuberculosis, 14 of which gave some degree of reaction with the Widal test; and 16 were diagnosed as negative for tuberculosis, 9 of which gave partial or complete Widal reactions. It would appear, from many of the histories received, that only a very superficial examination had been made of a large number of the patients. Without doubt, more of the patients were tuberculous than the tables indicate. At least, there must have been some suspicion of tuberculosis, since a tuberculosis-fixation test was requested. In 9 patients there was a history of typhoid fever and in 2 of typhoid vaccination. It would seem that advanced cases of tuberculosis are less likely to give positive Widal tests than the earlier cases. The effect of drying of the blood, as in dried blood specimens on parchment paper, apparently makes no difference with the reaction. The only other member of the typhoid-colon group of bacteria that was agglutinated by tuberculosis serums was *B. dysenteriae Flexner*. The macroscopic agglutination test, with both the Flexner and typhoid bacilli, gave negative agglutination reactions, although there was a precipitate somewhat simulating agglutination, but easily distinguished from it.

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THE AGGLUTINATION OF THE FLEXNER DYSENTERY BACILLUS BY THE BLOOD SERUM OF TUBERCULOUS PERSONS[1]

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We have reported observations on the Widal test in tuberculosis (1), in which we show that *B. dysenteriae Flexner* is agglutinated by serums from patients with incipient tuberculosis, while other members of the typhoid-dysentery-colon group are not agglutinated.

The Flexner bacillus has the advantage of giving as strong or stronger reactions than *B. typhosus*, at the same time giving fewer specific reactions, since the incidence of disease and vaccination against dysentery are much less commom than is the case with typhoid fever.

METHOD OF PERFORMING THE TEST

Blood from the patient is either drawn into a tube through a needle, and the serum separated and diluted 1 to 20 with physiological salt solution, or a drop of blood from the finger is taken on parchment paper and allowed to dry, being moistened later with sufficient distilled water so that the color is that of blood diluted about 1 to 20. The Flexner bacillus is grown on ordinary slanted agar tubes at room temperature for twenty-four hours, the growth being washed off with sufficient physiological salt solution to get a heavy suspension. A drop of diluted blood or serum is then mixed with a drop of culture (final dilution 1 to 40) on a cover glass, inverted over a vaseline ring on a concave slide and incubated at body temperature for one hour. The results have been read as "doubtful" in those specimens showing partial clumping with free rods still present, "positive" in those specimens in which the bacilli are completely agglutinated in small clumps and "strongly positive" when the bacilli are completely agglutinated in large clumps.

THE TEST ON NORMAL SUBJECTS

Thirteen apparently normal and healthy members of the laboratory force were bled from the finger and tested in the usual manner. Twelve

[1] From the Division of Laboratories, Illinois Department of Public Health.

were entirely negative while one gave a faint reaction. The thirteen were uniformly negative with *B. typhosus* run as a control. In repeating the tests with the Flexner bacillus by another worker using somewhat lower dilutions, 7 of the 13 individuals gave doubtful reactions. In none, however, was agglutination complete. It would seem, therefore, that dilution is an important factor and must be carefully controlled. One specimen of blood was received from the Veterans Bureau from an individual shown by a careful physical examination to be entirely free from tuberculosis. The test gave a negative reaction.

Thirty-four individuals, supposedly nontuberculous, at a State institution, were tested. Of these, 18 gave negative reactions, 10 doubtful, 3 positive and 3 strongly positive reactions. The histories of these patients were not obtained. Whether the positive reactions were due to undiscovered foci of tuberculous infection or to some other cause has not been determined.

THE TEST ON TUBERCULOSIS SUBJECTS

Three specimens from patients in advanced stages of tuberculosis at a sanatorium were tested in the usual manner. Two were negative and one was doubtful.

Eleven specimens were received from a tuberculosis clinic, as follows: 7 of pulmonary tuberculosis, active; 1 of pulmonary tuberculosis, incipient; 2 of tuberculosis of peritoneum; and 1 of tuberculosis of lymph nodes. All of these were negative except the last which gave a doubtful reaction.

The patient with incipient tuberculosis had been under treatment at the clinic for ten months. It would seem from these results that active and advanced cases of tuberculosis usually give a negative agglutination reaction with the Flexner bacillus. This corresponds to the results previously reported (1) in which the typhoid bacillus was used.

THE TEST ON SUSPECTED SUBJECTS

Daily there are submitted to the laboratories of the Illinois Department of Public Health a considerable number of blood specimens for the tuberculosis-fixation test. Serum from these specimens was separated and tested in the usual manner with the Flexner bacillus. Out of 161 specimens, 40 gave strongly positive reactions, 56 positive, 43 doubtful and 12 negative reactions, as shown in table 1.

It was desirable to get further histories from these patients, if possible. Hence, a questionnaire was sent to the physicians submitting the specimens. There were returned 58 answers sufficiently complete to be of service. Twelve patients had been diagnosed as definitely tuberculous by physical examination, 24 as indefinite and 22 as nontuberculous. The results of the tests are shown in tables 2, 3, 4 and 5.

Among the patients diagnosed as definitely tuberculous (table 2) by physical examination 9 (75 per cent) were positive by the agglutination test. Three of the nine showed tuberculosis other than pulmonary. The three doubtful tests were in cases of pulmonary tuberculosis.

TABLE 1

Agglutination reactions with 161 serums from individuals suspected for tuberculosis

Strongly positive	40
Positive	56
Doubtful	43
Negative	12

TABLE 2

Patients diagnosed tuberculous by physical examination

	PATIENT		AGGLUTINATION TEST	LOCALIZATION OF INFECTION AND REMARKS
	Sex	Age		
1	F	29	Strongly positive	Tonsillar fossa
2	F	34	Strongly positive	Sputum positive; active
3	M	9	Positive	Right tibia and femur
4	F	48	Positive	Active tuberculosis
5	M	28	Positive	Physical findings and sputum positive
6	F	26	Positive	Pelvis
7	F	22	Positive	Cicatrices of both lungs; quiescent
8	F	26	Positive	Quiescent
9	M	25	Positive	Quiescent
10	F	31	Doubtful	Chest; arrested
11	F	42	Doubtful	Arrested pulmonary tuberculosis
12	F	36	Doubtful	Active pulmonary tuberculosis

Among the patients diagnosed as indefinite for tuberculosis (table 3), 18 (75 per cent) gave positive agglutination tests. In all of these there was a suspicion of tuberculous infection, though a definite diagnosis had not been made. Three of the 24 reported intestinal trouble, while 2 were afflicted with bone or lymph node infections.

Of 22 patients (table 4) for whom a negative diagnosis of tuberculosis by physical examination was returned, 45 per cent were positive and 55

per cent doubtful or negative. It must be stated that many of these reports indicated by their brevity that a very hasty or incomplete physical examination had been made. Some of the individuals were in apparent health; others were suffering from various afflictions. In all, however, a tuberculosis-fixation test had been requested.

TABLE 3

Patients in whom a physical diagnosis of tuberculosis was indefinite

	PATIENT		AGGLUTINATION TEST	REMARKS
	Sex	Age		
13	M	22	Strongly positive	Sputum negative
14	F	16	Strongly positive	High temperature and rapid pulse
15	M	21	Strongly positive	Indefinite
16	M	18	Strongly positive	Slight mass right thigh anterior
17	M	52	Strongly positive	Dulness at apices
18	M	32	Strongly positive	Intestinal fermentation and gas, with fever
19	F	17	Strongly positive	Dulness in left apical region
20	F	29	Strongly positive	X-ray shows no positive evidence of pulmonary tuberculosis
21	M	59	Strongly positive	Indefinite
22	M	50	Positive	Husky voice and weak condition
23	F	23	Positive	Rapid pulse and loss of weight
24	M	32	Positive	Ulcer of duodenum
25	F	32	Positive	Tuberculous salpingitis
26	M	26	Positive	No definite symptoms of tuberculosis
27	F	29	Positive	X-ray shows no positive evidence of pulmonary tuberculosis
28	F	60	Positive	Indefinite
29	F	42	Positive	Indefinite; focus not found
30	F	35	Positive	Right apex
31	M	44	Doubtful	Right apex; clinical picture suggests tuberculosis
32	M	15	Doubtful	Enlargement of cervical, epitrochlear and inguinal lymph nodes
33	F	28	Doubtful	Slight fever, weak, lack of ambition
34	F	50	Doubtful	Colitis since 1910
35	F	65	Negative	Died shortly afterward with chronic valvular heart disease
36	M	60	Negative	Wassermann 4 plus

DISCUSSION

It must be remembered that infections with the Flexner dysentery bacillus are not uncommon and that carriers to a greater or less extent exist in the general population. Agglutination reactions with serums from such individuals must be expected with the Flexner bacillus. Other

diseases and infections, as well as tuberculosis, may likewise give a positive agglutination reaction with the Flexner bacillus. This is a point to be worked out in the near future. On the other hand, there appears

TABLE 4

Patients in whom the physical diagnosis was reported negative for tuberculosis

	PATIENT		AGGLUTINATION TEST	REMARKS
	Sex	Age		
37	F	35	Strongly positive	In excellent health
38	F	48	Strongly positive	Chronic hepatic disorder
39	F	Infant	Strongly positive	Colon bacillus pyelitis
40	M	37	Strongly positive	No history
41	M	17	Positive	Severe acne roseola of face
42	F	24	Positive	Pregnant; in best of health
43	F	22	Positive	Slight peribronchial infiltration
44	M	67	Positive	Mouth lesions of syphilis
45	M	30	Positive	No suspicion of tuberculous infection
46	F	50	Positive	No symptoms of tuberculosis
47	M	20	Doubtful	Chest negative for tuberculosis, no cough, no fever
48	M	50	Doubtful	Dizziness, weakness, loss of vigor
49	F	Infant	Doubtful	Same patient as no. 39
50	F	17	Doubtful	Recovering from pneumonia
51	F	23	Doubtful	Died from aortic and mitral valvular disease
52	M	18	Doubtful	Diarrhea, bronchitis
53	M	28	Doubtful	Slight alopecia
54	F	48	Doubtful	Lethargic encephalitis
55	M	22	Doubtful	Paralysis of 3rd cranial nerve
56	M	37	Doubtful	Negative
57	M	21	Doubtful	Manic depression psychosis
58	F	40	Negative	No symptoms

TABLE 5

Summary of results of agglutination tests on individuals suspected for tuberculosis

	TOTAL	AGGLUTINATION TEST		
		Positive and strongly positive	Doubtful	Negative
Positive physical diagnosis of tuberculosis	12	9 (75%)	3 (25%)	0
Indefinite physical diagnosis of tuberculosis	24	18 (75%)	4 (17%)	2 (8%)
Negative physical diagnosis of tuberculosis	22	10 (45%)	11 (50%)	1 (5%)

to be a substance in the blood of many individuals which causes an agglutination of the Flexner bacillus (as well as the typhoid bacillus) and persons in the incipient or early stages of tuberculosis are among those that give this reaction. Porter (2), who for some years has been making a tentative diagnosis of tuberculosis on the strength of the peculiar Widal reaction obtained with tuberculous serums, states that, in every case so reported that could be followed up, a focus of tuberculous infection was found within two months afterward. It seems, therefore, that persons that give positive agglutination tests with the Flexner bacillus should be carefully examined before tuberculosis is ruled out.

CONCLUSIONS

1. Persons in the incipient stage of tuberculosis apparently carry in the blood a substance capable of agglutinating the Flexner dysentery bacillus.

2. Persons in the advanced stages of tuberculosis, as well as normal persons, as a rule do not react to this test.

3. The dilution of the blood serum apparently affects the results, normal persons reacting in some cases with dilutions of less than 1 to 40.

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THE QUESTION OF THE MOST RELIABLE AUSCULTATORY SIGNS IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS[1]

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Physical signs play an important rôle in the diagnosis of clinical pulmonary tuberculosis. However, the relative values of the various signs heard during auscultation have not been definitely determined or largely accepted by the profession. For this reason I have analyzed a series of cases to see to what extent, when my methods and standards of interpretation were used, such changes in breathing as moderate bronchovesicular, distant, exaggerated or bronchovesicular breathing with increased vocal resonance (whispered voice), when occurring without the presence of râles, were accompanied by definite parenchymatous changes in the X-ray and a definite diagnosis of clinical pulmonary tuberculosis. In a similar manner the presence of râles, regardless of breath sounds, was analyzed.

Perhaps not many clinicians would interpret the physical signs heard upon auscultation in any single case in an identical way unless the changes were quite marked. Many clinicians likewise determine the auscultatory physical signs under differing methods of breathing. However, most examiners have, in their own mind at least, a standard of interpretation which is arrived at through a standard method of examination. The individuals in this analysis were examined for breath sounds in the sitting position on a stool and were told to breathe through their mouth. No effort was made to control intensity or rhythm.

All breath sounds were interpreted as normal unless it was thought that some pathological pulmonary condition existed. The cases were divided into the following groups:

1. Those in which supposedly abnormal bronchovesicular breathing, usually accompanied by an increase in whispered voice, occurred without râles. This group was composed of 248 cases.

[1]Read before the American Climatological and Clinical Association, Niagara Falls, New York, May 23, 1923.

2. Those in which there were no abnormal breath sounds nor râles, 45 cases.

3. Those having distant or exaggerated breathing with no râles, 13 cases.

4. Those in which moderately coarse or fine râles were indefinitely present (questionable râles) the breath sounds being disregarded, 36 cases.

5. Those in which râles were heard but not in the upper one-third, breath sounds disregarded, 93 cases.

6. Those in which fine râles were heard in the upper one-third, with râles present or absent elsewhere, breath sounds disregarded, 140 cases.

7. Those in which moderately coarse râles were heard in the upper one-third with râles present or absent elsewhere, breath sounds disregarded, 425 cases.

In group 1 (bronchovesicular breathing) composed of 248 cases, clinical pulmonary tuberculosis was diagnosed in 59 per cent.

In group 2 (breath sounds unchanged) 45 cases, clinical pulmonary tuberculosis was diagnosed in 60 per cent.

In group 3 (breathing distant or exaggerated) 13 cases, clinical pulmonary tuberculosis was diagnosed in 67 per cent.

In group 4 (râles indefinite) 36 cases, clinical pulmonary tuberculosis was diagnosed in 72 per cent.

In group 5 (râles not in upper one-third) 93 cases, clinical pulmonary tuberculosis was diagnosed in 78 per cent.

In group 6 (fine râles in upper one-third) 140 cases, clinical pulmonary tuberculosis was diagnosed in 82 per cent.

In group 7 (moderately coarse râles in upper one-third) 425 cases, clinical pulmonary tuberculosis was diagnosed in 99 per cent.

From this analysis it is readily seen that, as far as diagnosis is concerned, the standards of interpretation used by me were only a little more than one-half efficient when only bronchovesicular breathing was heard. The finding of bronchovesicular breathing interpreted as abnormal was no more likely to be associated with clinical pulmonary tuberculosis than when no breath changes were heard, providing, of course, râles were not heard in either instance.

Distant or exaggerated breathing, occurring alone, was accompanied by a larger percentage of positive diagnoses than when either of the above occurred. It is only when râles appear that it can be said that diagnosis reaches such a percentage of positives as to make their finding

relatively consistently valuable. This is demonstrated in *groups 6* and *7;* the moderately coarse râles, in the upper one-third, from this analysis being the most valuable in diagnosis, inasmuch as nearly all cases in which they occurred were diagnosed as having clinical pulmonary tuberculosis.

Definite parenchymatous X-ray changes were demonstrated in the various groups as follows:

Group 1: (bronchovesicular breathing) 40 per cent.

Group 2: (unchanged breath sounds) 51 per cent.

Group 3: (distant or exaggerated breathing) 31 per cent.

Group 4: (indefinite râles) 53 per cent.

Group 5: (fine or moderately coarse râles not in upper one-third) 67 per cent.

Group 6: (fine râles in upper one-third) 78 per cent.

Group 7: (moderately coarse râles in upper one-third) 98 per cent.

Here it is also clearly shown that bronchovesicular breathing, as interpreted by me, is by itself not a reliable guide to the presence of parenchymatous lung changes. It is also clearly shown that one-half of those having no abnormal breath sounds or râles could or did have parenchymatous lung changes; thus making a negative lung examination by physical signs practically of no value. When râles occur, however, I can be quite certain of the existence of parenchymatous lung changes in the X–ray films, and particularly so when moderately coarse râles are found in the upper one-third.

Tubercle bacilli were found at the Sanatorium as follows:

Group 1: (bronchovesicular breathing) 18 per cent.

Group 2: (breath sounds unchanged) 22 per cent.

Group 3: (distant or exaggerated breathing) 0.

Group 4: (indefinite râles) 19 per cent.

Group 5: (râles not in upper one-third) 43 per cent.

Group 6: (fine râles in upper one-third) 45 per cent.

Group 7: (moderately coarse râles in upper one-third) 71 per cent.

From the above it can be said that when moderately coarse râles are heard the lesion is probably an open one.

Of course, it can easily be said that all the cases in these analyses presumptively had clinical pulmonary tuberculosis and do not represent the occurrence of bronchovesicular breathing, interpreted as abnormal, in the ordinary run of cases undergoing chest examinations.

Nevertheless, only 59 per cent were diagnosed as having the disease. A much more important criticism is that the standards for examination and interpretation were faulty. Undoubtedly they were. Can one, however, make the standard so exact as to be more valuable? Does my standard fall far below the average? I do not think so.

It is likewise true that most of the cases in which I found abnormal bronchovesicular breathing had this change at the upper part of the right lung. But is it not also true that here pulmonary tuberculosis is

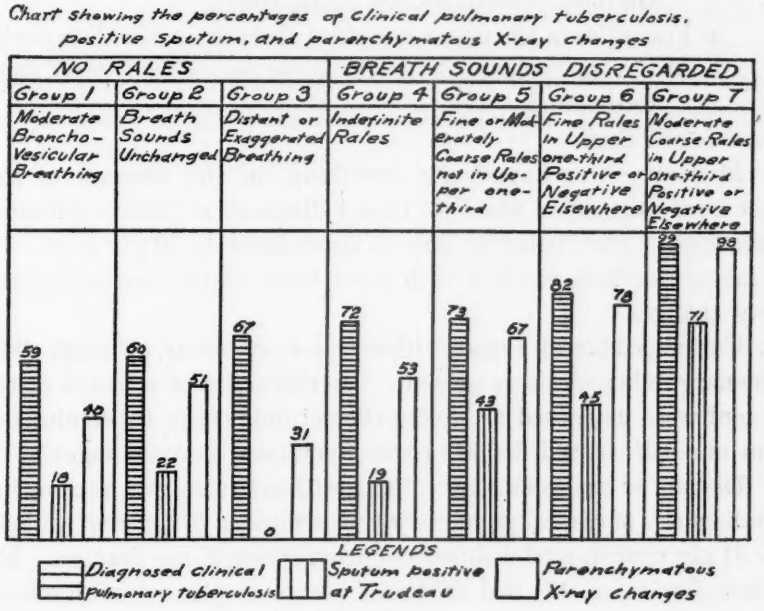

CHART 1

most likely to first show itself? How differentiate between the slightly abnormal bronchovesicular breathing heard over diseased areas and the normal br nchovesicular breathing due to anatomic structure? Râles permit of only a much narrower margin of interpretation and signify some pathological change. In my experience, at least, they are the only auscultatory physical sign of any importance in the diagnosis of pulmonary tuberculosis unless breath sound changes are so marked as to approach the bronchial type.

SUMMARY

From an analysis of cases presenting

1. Bronchovesicular breathing, interpreted as abnormal and without râles.
2. Unchanged breath sounds with no râles.
3. Distant or exaggerated breathing with no râles.
4. Indefinite râles.
5. Fine or moderately coarse râles elsewhere than in the upper one-third (breath sounds disregarded).
6. Fine râles in the upper one-third (breath sounds disregarded).
7. Moderately coarse râles in the upper one-third, (breath sounds disregarded).

it was found that

1. Moderate bronchovesicular breathing, in the absence of râles, is not a safe sign upon which to base a diagnosis of clinical pulmonary tuberculosis. The chance of error is approximately 50 per cent. Furthermore, less than one-half such cases have definite parenchymatous X-ray changes.

2. Unchanged breath sounds without râles may occur, although clinical pulmonary tuberculosis is present. In this series of selected cases 60 per cent were diagnosed as having clinical pulmonary tuberculosis and about one-half showed definite parenchymatous X-ray changes.

3. Distant or exaggerated breathing without râles was accompanied by a diagnosis of clinical pulmonary tuberculosis in 67 per cent, although only 31 per cent showed definite parenchymatous X-ray changes. Most of these few cases (13) had thickened pleura or pleurisy with effusion.

4. When râles occur, however, some definite pulmonary pathological change is most likely to be present. Regardless of breath sounds, when râles were heard, clinical pulmonary tuberculosis was diagnosed in 78 to 99 per cent of the cases, depending upon the location and type of râle heard. The X-ray showed definite pulmonary parenchymatous change in 67 to 98 per cent, also depending upon location and type of râle.

CONCLUSIONS

Using my own standards of interpretation and method of examination I have found.

1. That moderate changes in breath sounds are too often found, when clinical pulmonary tuberculosis cannot be diagnosed, to be of value in the diagnosis of this disease. Particularly is this true of bronchovesicular breathing.

2. That a negative physical examination of the chest by no means rules out clinical tuberculosis. A negative examination has about the same value as the occurrence of bronchovesicular breathing.

3. That râles heard especially in the upper portion of the lung, and particularly the moderately coarse râle, is a very reliable diagnostic sign of clinical pulmonary tuberculosis. As a matter of fact, it is the only reliable auscultatory sign unless the changes in breathing are very marked. It is not to be inferred from this, however, that whenever râles are heard clinical pulmonary tuberculosis is always present.

A CASE OF HYDROPNEUMOPERICARDIUM IN A TUBERCULOUS INDIVIDUAL DURING AN ATTACK OF TYPHOID FEVER[1]

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Hydropneumopericardium is, as all are aware, a rarity of medicine; so rare that it might almost be said to be a curiosity. Many engaged for years in active practice have not encountered a single instance. Medical literature contains accounts of about only 44 cases. Most of these were summarized by Walter B. James (1) in 1904, in an article describing a case of his own and mentioning 37 other reports. Since then Cowan, Harrington and Riddle (2) in 1913 reported 5 additional cases, and in 1918 Stewart (3) reported another.

From the reports of James, and Cowan, Harrington and Riddle, the following interesting facts are extracted:

In 34 instances there was an opening from the pericardium to some other viscus. This opening was largely due to trauma. In 9 the puncture came from without. Among direct causes may be mentioned the swallowing of bone and false teeth, "sword swallowing," fracture of ribs or sternum, paracentesis of pleura, cancer of esophagus, softening of tuberculous focus (lymph node), emphysema, pneumonia, gangrene, empyema, hepatic abscess, gastric ulcer, appendicitis, facial erysipelas with "sore throat," and pericarditis.

In only a few cases was an accompanying pericarditis absent. Infection with effusion, which later became purulent, occurred in the majority.

The fluoroscope or X-ray was used for diagnosis in only 4 of the cases. This was due mostly to the fact that most of the cases occurred before the discovery and use of the X-rays.

Physical signs led to a correct diagnosis during life in 37 instances. Usually the apex impulse disappears, the area of cardiac dulness is replaced by tympany, the heart sounds become distant and, when effusion develops, a "rhythmic, splashing, churning, friction" sound (James), *le bruit de la roule hydraulique*

[1] Read before the American Climatological and Clinical Association, Niagara Falls, New York, May 23, 1923.

(waterwheel sound), is noticed. The tympanitic note is replaced by fluid dulness and vice versa upon change of position of the patient.

Symptomatically, there are usually cyanosis, precordial oppression and syncope. In our case the heart sounds were audible to the patient and to anyone twelve inches from him, without the use of the stethoscope.

The condition is by no means always fatal, as 16 of 45 cases (44 + ours) recovered (36 per cent).

Our case occurred at the Trudeau Sanatorium during an epidemic of typhoid fever which has been reported elsewhere (4). Unfortunately, no X-ray picture was taken because it was thought that the patient was too ill to risk moving to the X-ray department in another building and no portable apparatus was then available. Following is the detailed history of the case:

Case 4669: Mr. C. W. H., admitted March 31, 1917, male, aged 26, single, bookkeeper. Family history negative for tuberculosis, cancer, heart and kidney disease. No history of exposure to tuberculosis. In October, 1916, symptoms of pulmonary tuberculosis were noticed, followed in December, 1916, by hemoptysis of an ounce, which was later repeated and followed by streaked sputum for two weeks.

Examination revealed tuberculosis of the right lung in the upper two-thirds and the left lung to the clavicle. Tubercle bacilli were found in the sputum. The X-ray revealed no unusual enlargements at either hilum.

While undergoing treatment nothing unusual occurred. After four months the patient was discharged with definite improvement. He was a quiescent case. He was then employed at the Sanatorium as bookkeeper. He remained well for another month, when on August 24, 1917, he complained of headache and malaise. Temperature on this day normal. August 25th the temperature gradually rose, "biliousness," nausea, etc., occurred and, as there were other cases of typhoid at the Sanatorium at that time, a provisional diagnosis of it was made, and this was later confirmed by finding typhoid bacilli in the blood and feces. The patient was never very toxic, the spleen was never enlarged. Fever subsided in twenty-two days and the patient went on to complete recovery.

On September 5th, 1917, the eighth day of the typhoid fever, the patient complained of pain in the left chest and shoulder and that he could hear his heart beat when he turned on his left side. Examination of the precordia showed very faint heart sounds in the recumbent position. The area of of cardiac dulness was not increased. When the patient turned on his left side or took a semirecumbent position, a distinct rough pericardial friction rub

was heard. In two days cardiac dulness was replaced by resonance and a distinct pericardial splash was heard. The friction rub was still present. On the third day hyperresonance replaced dulness when the patient was recumbent. When lying on his right side dulness was present to the left sternal margin. Friction sound and gurgle were still present. On the fourth day the patient said he could feel the cardiac splash on changing his position. The heart sounds on this day in the third and fourth interspaces were heard chiefly during inspiration. During expiration they almost disappeared. Along the right border of the heart the sounds were loud to the nipple line. Dulness was present to the right of the sternum when the patient was on his right side. When he turned on his left side a splash was heard, followed later by a friction rub. The patient was still conscious of the friction rub.

On the sixth day there was no palpable or visible impulse over the precordium. The normal area of cardiac dulness was replaced by hyperresonance. With the patient on his back the heart sounds were indistinct. The first sound was heard best in the third interspace, 3 cm. to the right of the sternum. The aortic second sound was heard fairly distinctly at the base. The second pulmonic sound could not be heard. With the patient on his left side a distinct to and fro friction sound was heard in the fifth interspaces, 7 cm. from the midsternal line. This sound was followed by a splashing sound which was accentuated by shaking the patient and made audible to the ear at a distance of 6 to 8 cm. from the chest. The area of cardiac dulness was not changed.

With the patient on the right side there was a definite impulse in the right third interspace. No shock or thrill was felt. The area of cardiac dulness was not changed but dulness was intensified. Heart sounds at the base were more distinct. The first sound was audible in the fifth interspace, 7 cm. from the midsternal line.

On the tenth day the patient complained of a "heart knock sound" when lying on his back and while holding his breath at the end of expiration. Auscultation revealed a loud liquid knocking sound over the precordium, which disappeared when the patient resumed breathing. On the thirteenth day the "knock" and "splash" became less audible. On the fourteenth day relative cardiac dulness returned to normal and the heart sounds were distinctly heard. Breath sounds in the lower left axilla, which were somewhat distant from the outset, were now more distinctly heard. On the nineteenth day a palpable impulse was present in the left sixth interspace. Absolute cardiac dulness was restored. The heart sounds were normal.

At no time during this illness did the patient have cardiac or respiratory distress. Cyanosis was not present. For the typhoid fever the patient was given a modified Coleman high caloric diet, with fluids sufficient to produce free elimination of urine. For the pericardial condition an icebag was used over the heart from the first to fourteenth day. Recovery was uneventful,

the pulmonary tuberculosis was not aggravated and the patient was discharged October 24th (two months after the onset of typhoid and forty days after onset of hydro-pneumo-pericardium). He has since remained well (1922).

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TUBERCULIDS[1]

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The term *tuberculid* was first used by Darier, to describe a group of skin lesions associated with tuberculosis of the viscera, which, while an accompaniment of tuberculosis, did not exhibit, necessarily, the characteristic pathological anatomy of tuberculosis in other structures.

The *papulonecrotic tuberculid*, which is now generally accepted as of tuberculous origin, is a skin lesion which consists of multiple papules, varying in size from that of a pinhead to several centimetres in diameter, and having a tendency to occur in successive crops. The individual papule is characterized by a necrotic centre. In the early stage it may take the form of a vesicle which dries, leaving the central necrosis. The centre may discharge pus or be picked out, leaving a conical depression. Later, in most cases, a punctate atrophic scar remains, which is usually surrounded by an area of increased pigmentation.

Largely as a matter of convenience for study, the papulonecrotic tuberculid is divided into two types, (1) *acinitis*, which occurs on the face and ears, and (2) *folliclis*, which occurs on the extremities. The papulonecrotic tuberculid may occur anywhere on the body, but its favorite site is on the extremities, especially on areas exposed to trauma, as the fingers. The *erythema induratum* of Bazin is also pretty generally accepted as being of tuberculous origin, It is an ulcerative lesion occurring on the legs, principally the calf. Tubercle bacilli have been isolated from these ulcers by both the antiformin method and guinea pig inoculation. Stokes speaks of erythema induratum as being possibly a form of the papulonecrotic tuberculid, the papules being conglomerate or of an extreme size. *Lichen scrofulosorum*, which is a grouped follicular papular eruption occurring on the trunk, has been demonstrated clinically and experimentally to be a true tuberculid. This lesion is regarded as a generalized form of the papulonecrotic tuberculid.

[1] Read before the Trudeau Society of Los Angeles, November 22, 1922.

[2] Of the Monrovia Clinic (formerly Kalb and Kirschner Cottages).

According to Stokes other lesions now held to be of tuberculous etiology include the following: *acne scrofulosorum, pityriasis rubra pilaris,* certain *exfoliative erythrodermias, acne necrotica, acne cachecticorum, lupus pernio* and the *sarcoids.* There is also a strong suspicion that *lupus erythematosus, purpura* and *erythema nodosum* are of tuberculous etiology.

While these various skin lesions may occur separately, the different forms are very often found present at the same time, or occurring at different times in the same individual. While they may develop during an apparent activity of the tuberculous infection their appearance may precede this activity by several months or even years. As a rule, the presence of the accompanying systemic tuberculosis is detected largely through objective findings at the time of the occurrence of these skin lesions.

In Stokes's series of 30 cases of papulonecrotic tuberculids and associated skin conditions, only 5 had been correctly diagnosed previously, and in these a systemic tuberculosis, as suggested by the skin manifestations, had not been suspected. Stokes states that four-fifths of the diagnostic errors are due to unfamiliarity with the lesions, failure to observe them, or of a tendency to consider a tuberculid syphilitic. In over one-third of his cases the lesions had been ignored or overlooked; in one-third wrongly diagnosed; 6 were diagnosed as syphilis because of a positive Wassermann and one as Reynaud's disease; one varicose ulcer and one psoriasis. Eighty per cent of the cases were in women, from ten to fifty-one years of age. Eighty-three per cent had evidence of past or present papulonecrotic tuberculosis. In 3 the lesions were on the face, in 12 on the hands, in 15 on the legs, in 9 on the trunk, while in 2 there was erythema induratum unaccompanied by any other tuberculid. One of these cases had tuberculous lymph nodes, and one *verrucosa cutis tuberculosa.*

In one-fourth of Stokes's cases there was a family history of tuberculosis. In one-third of the cases the diagnosis of tuberculosis had been previously made, principally from the presence of lymphadenitis. In 57 per cent there were unquestionable objective signs of tuberculosis, and strongly suspicious signs in an additional 13 per cent. In 30 per cent there were no definite signs of tuberculosis, but the patients were for the most part underweight and anemic. Thirty-three per cent had slight, but positive X-ray findings, and another 33 per cent showed physical signs in the lungs suggestive of tuberculosis. In

only 17 per cent, however, were there both physical and X-ray signs of tuberculosis in the lungs. There were visible or palpable lymph nodes in 66 per cent, while 38 per cent had a marked lymphadenitis. There was one case each of sacroiliac abscess, tuberculous peritonitis, renal tuberculosis and tuberculous verrucosa cutis and three had a tuberculous keratitis.

I have recently seen three cases of the folliclis type of the papulonecrotic tuberculid.

Case 1 was a nurse seen in March, 1921, thirty-one years old and on duty in a tuberculosis sanatorium. She was moderately anemic and, as she stated, "generally run-down." She gave a history of cervical lymphadenitis dating back about three years. The enlarged nodes had been removed twice, the last time about two years before. She had a crop of papular lesions, with necrotic centres, over the palmar and dorsal surfaces of the terminal phalanges of both hands, the lesions being most marked on the dorsal aspect. The year before she had had a similar eruption which lasted from six to eight weeks. Shortly after I saw her she was called to Mexico and I did not have an opportunity to follow up the case.

Case 2 was a man aged twenty-eight, a former bank clerk, seen in March, 1922. He had a history of active pulmonary tuberculosis for about eighteen months, with left-sided penumothorax. The eruptions were on terminal phalanges of both hands, confined for the most part to the dorsal surface. There were a few faint scars of a previous eruption which had occurred in the spring of 1921. As this was a progressive case of pulmonary tuberculosis and the skin lesions were not especially troublesome, there was nothing in particular done for them except to keep them under observation, and they cleared up in about six weeks.

Case 3 was a school teacher, married, age 32. She was also seen in March, 1922. For the previous three years she had been living with her husband who had active pulmonary tuberculosis. She stated that she had felt tired and had been underweight for the past twelve or eighteen months. A few months before I saw her she had been examined rather thoroughly for tuberculosis and had been pronounced negative. She gave a history of chronic maxillary sinusitis. The eruption was on the dorsal surface of the terminal phalanges of both hands. This eruption had recurred in the spring and fall for the past three years, lasting each time about six weeks. After I had explained to her the nature of her ailment she gave up teaching and returned to her home in Oregon. When I last heard from her she said that she was very nervous and miserable.

Each of these three cases had been seen by a number of physicians whose work was largely devoted to tuberculosis, and the diagnosis had been all the way from simple dermatitis to syphilis and leprosy. In no case had it been suggested to the patients that their eruptions were of a tuberculous nature.

Stokes reported a separate series of 8 cases in which were associated *purpura, erythema multiforme* and *erythema nodosum.* Purpura was present in 3; erythema multiforme in 3; and erythema nodosum in 6. Four of these cases were definitely tuberculous and the remaining 4 highly suspicious.

In 1915 Rosenow demonstrated a polymorphous gram-negative diphtheroid microörganism as the cause of erythema nodosum. Stokes calls attention to the fact that some of these skin conditions may, and undoubtedly do, have a multiple etiology and that we must not forget their possible connection with tuberculosis. He feels that, although certain of the more acute forms of erythema nodosum are due to the Rosenow organism or perhaps to the streptococcus, there is a more subacute type of this lesion produced by the tubercle bacillus or its products; and he concludes that all cases of erythema nodosum should be subjected to periodic observation and examinations, and that, even in the presence of a possible infection from a pyogenic focus, the likelihood of a tuberculous etiology should be seriously entertained.

In 1907 Abt suggested that erythema nodosum prepared the way for tuberculosis. In 1914 Foerster reported 2 cases of erythema nodosum associated with tuberculosis. Since that time Nicoli reported 6 such cases and Jaquered 2. Many French writers have done considerable work along this line and they regard erythema nodosum as being of tuberculous etiology. Landouzy and Brain successfully inoculated guinea pigs with material from the lesions of erythema nodosum.

I have had 2 cases in which erythema nodosum occurred in connection with tuberculosis.

Case 1 was a school girl, about seventeen years old, who gave a history of an indefinite pain in the lower lumbar region. When first seen she had numerous red areas, varying in size from a dime to that of a quarter, over both anterior tibial surfaces. They were slightly raised and showed a tendency to become confluent. She had some joint and muscle pain, especially in the extremities. She was anemic and generally run down. Her tonsils harbored a subacute infection. She was put to bed on salicylates. Her temperature rose to 102° for ten days or two weeks. In three weeks the lesions had cleared

up and she returned to school. A few months later her appendix was removed and this proved to be tuberculous. Against my advice she continued her course in school. Two years later she developed pulmonary tuberculosis. After a year of sanatorium life she again returned to school and at the end of another year consulted an orthopedist who found a rather extensive tuberculous involvement of the lower dorsal spine.

Case 2 occurred in a patient in a sanatorium. This was a young man, aged twenty-six, with moderately advanced, active pulmonary tuberculosis. His temperature, which had been normal, rose to 103°, and reached this every afternoon for about two weeks; there was considerable pain in leg muscles and joints. He was put on salicylates and kept in bed, when the lesions disappeared in about three weeks. The pain also subsided, his temperature returned to normal and there was apparently no change in his lung condition.

Considerable stress has been laid upon the appearance and the significance of tuberculids in children. Maurice L. Blatt, of Chicago, in a review on tuberculous lymphadenitis in children, speaks of the relatively common occurrence of accompanying tuberculids.

A. Gesmondi, in an article abstracted in the *Journal of the American Medical Association* in December, 1918, says, "The papulonecrotic tuberculid may be the only sign of tuberculosis in infants and older children and by recognizing this many puzzling cases can be cleared up." Cooke and Hemplemann, of Washington University, in a paper on "Masked Juvenile Tuberculosis" state that the papulonecrotic tuberculid, lichen scrofulosorum and phlyctenular keratitis and conjunctivitis attracted their special attention inasmuch as these affections are known to bear a close relation to tuberculosis. Fishberg quotes Hemplemann as stating that tuberculids were present in over 20 per cent of a series of tuberculous infants. Hans Much, in his recent book on "Tuberculosis of Children," states that the tuberculids should be looked for in early life when they are of frequent occurrence, as they are always the expression of active tuberculosis. Wollstein and Spence found tuberculids present in only 4 of 180 cases of tuberculosis in infants and children.

The exact methods by which these skin lesions are produced is not clearly understood. Stokes favors the opinion that they are the result of hematogenously distributed tubercle bacilli, which tend to form emboli in terminal vessels especially. Efforts to isolate the bacilli from these foci have been unsuccessful except in a very few cases. This

is thought to be due to the fact that the bacilli are destroyed by the resulting inflammation.

Septic foci and various acute conditions, like pneumonia, grippe, rheumatism, tonsillitis and pleurisy, were present in from 40 to 70 per cent of Stokes's cases and appeared to have an exciting or predisposing influence. Through the influence of the bacteria and bacterial poisons from these septic foci and acute conditions there is thought to result a certain allergy or hypersensitiveness of the skin, predisposing to the formation of the tuberculid by the tubercle bacillus and the various forms are the result of a variation in the allergy or hypersensitiveness. Stokes substantiates this view by stating that "evidence of the ability of septic foci to produce or predispose to dermatosis, urticaria, and similar expressions of cutaneous hyperirritability are accumulating."

The removal of these septic foci or the clearing up of the acute conditions does not cure or prevent the recurrence of these skin lesions. This could perhaps be explained by assuming that the hypersensitiveness of the skin which they produce remains.

Stillians, of the Dermatological Department of Northwestern University, is of the opinion that the lesions are caused either by the localization of tubercle bacilli of attenuated virulence or by a few bacilli of normal virulence which are overcome by the resistance of the skin and make their detection by animal inoculation impossible. Much says, "They originate through partigens which become free in the changing conditions of combat between body and bacilli and are a symptom of oversensitiveness." The opinion has also been offered that these various forms of tuberculids are the result of various hereditary conditions of the skin.

Though lymphadenitis or lymphatic infection is the most common, there is no constant relation between the type of tuberculous focus and the type of skin lesion which results.

In the diagnosis of tuberculids we must depend largely upon a familiarity with the lesions, as they occur for the most part in patients in whom the evidence of a tuberculous focus is lacking or obscure.

Stokes mentions the constitutional symptoms as consisting mostly of a moderate secondary anemia, mild leucopenia, occasional afternoon elevation of temperature and moderate loss of weight, with rheumatic symptoms in about 50 per cent of his cases. There was noticeable lack of cough, expectoration, night sweats and hemorrhage and, not infrequently, the patients were of the robust type. The frequent

accompaniment of myalgia and arthralgia readily leads to the diagnosis of a rheumatic condition. Again, inasmuch as many of these cases give repeated positive Wassermann tests, of varying degree, and at the same time clear up under arsphenamin treatment, the diagnosis of syphilis is frequently made.

Acinitis, the papulonecrotic tuberculid of the face, may be confused with acne vulgaris or variola. Folliclis, the papulonecrotic tuberculid of the extremities, may be confused with dysidrosis, lupus pernio or, when there is vasomotor disturbance, with Reynaud's disease.

When the necrotic papules occur on the trunk they may lead to confusion with furunculosis, severe acne vulgaris or nodular lues. Scratch papules, lichen urticaria and the nodules of Hodgkin's disease may also cause confusion. The general distribution of the papulonecrotic tuberculid may be mistaken for pustular lues. Erythema induratum, when it occurs alone, as it seldom does, may suggest nodular lues, gumma, multiple infarction of the skin, anemic ulcers and areas of gangrene. The ulcerative erythema induratum may resemble ulcerative lues, varicose ulcer and epithelioma.

In considering the differential diagnosis of these conditions there are some characteristics peculiar to the papulonecrotic tuberculids which should be borne in mind. Their general tendency is to occur with periodicity, especially in the spring, and to a less extent in the fall. They come in successive crops. The lesions vary in size from small papules to several millimetres in diameter. They are raised above the surface and are not ordinarily painful, but when pressure is exerted over their surface there is a feeling as though a thorn was being pressed into the flesh. The eruptions, as a whole, last from four to eight weeks and, on clearing up, leave characteristic scars. These scars, I believe, are at times hard to define, so that an inquiry should be made as to the possible history of previous eruptions.

In discussing the treatment of these conditions I wish only to say a few words in regard to the way in which they are handled by Stokes. I feel that this will be of interest, not only from the standpoint of the cutaneous lesions themselves, but may shed some light upon the treatment of certain tuberculous foci. Stokes says that the "surgical treatment of the tuberculous focus, as ordinarily carried out, neither guarantees the patient against a subsequent tuberculid nor offers him any worthwhile therapeutic prospect for one already present." The X-ray was effective in the reduction of lymph nodes, but its effect on the general

condition of the patient or on the cutaneous lesions was not marked. The use of tuberculin failed to secure any marked benefit and in some cases resulted in unfavorable reactions with extension of the trouble. The use of iron in those cases with marked anemia appeared to be especially beneficial. The intravenous use of arsenic in the form of arsphenamin gave the most satisfactory results. This was combined with the X-ray, when possible, in the cases of tuberculous lymphadenitis, and with an antituberculosis outdoor regimen, diet, removal of secondary foci of pyogenic infection when possible and the correction of stasis and vasomotor abnormalities in the extremities. Rest was used only in a relative degree. None of the patients was put to bed and some of them were allowed to continue their occupations.

Stokes feels that the arsphenamin is the principal factor in bringing about improvement. He says that the improvement effected in the tuberculid by the administration of arsphenamin is often the first change apparent under the treatment. Usually with the first and second injections, but sometimes not until the fourth, there is marked drying and reduction in size of any active lesion present and a dimunition of tenderness. Stokes adds that, on the other hand, a number of his patients showed definite improvement in general symptoms while receiving the first course of injections, and this in spite of the fact that some resumed hard work to which they had been physically unequal prior to their first course of treatment. He concludes that the action of this drug does not suggest that of a specific bactericidal agent, but rather that of a fortifier of individual resistance and a means of stimulating the defensive mechanism of the body against the tubercle bacillus. He thinks that the arsenic is stored in the liver so as to provide a prolonged tonic effect. With this treatment only 12 per cent of 20 of his cases failed to show a marked improvement as evidenced by complete disappearance of the tuberculids or a marked reduction in their severity, coupled with a gain in weight, improvement in general appearance and disappearance of rheumatic symptoms. The use of arsenic in the febrile, acute, or rapidly progressive cases is not advised. The arsphenamin is given intravenously at weekly intervals. The first course is usually six injections, the initial dose is 3 decigrams, and the average dose 4 to 5 decigrams. The arsenic is given in courses because of its cumulative effect. The subsequent courses may be shorter. Stokes found that by estimating the total dosage in terms of grams of arsphenamin an apparent relation between the total dosage ranged from 3.8

to 10.8 gm., the latter dosage being considered high for the average case. He advises the repetition of the course as a seasonal reinforcement of the patient at the times of the year, in March and November, when the tendency to recurrence is greatest. He calls attention to the fact that the patients with tuberculids appear to have a special idiosyncracy to arsphenamin, which was present in 50 per cent of his cases, and he warns against the signs of a definite overtreatment syndrome.

In conclusion, I believe with Hans Much that "the subject is far too little known and understood." I feel that the lesions which are recognized to-day as true tuberculids and many other associated skin lesions, the relation of which we now do not clearly understand but which are suspected of being tuberculous in origin, are sufficiently common to warrant more thorough consideration and study. I believe, especially, that a closer collaboration of the general diagnostician and the tuberculosis specialist with the dermatologist would be valuable in clearing up the position which these skin lesions occupy in the medical field, with the result that we would acquire definite assistance in the diagnosis, prognosis and treatment of many obscure cases.

SPONTANEOUS PNEUMOTHORAX

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In the issue of the *Journal of the American Medical Association* for December 30, 1922, there appeared an article on "Spontaneous Pneumothorax" with the report of a case by McDonnell. I feel that this article gives rise to wrong impressions regarding this condition.

In discussing the subject we ought first to endeavor to arrive at a definite conclusion as to what we mean by the term *spontaneous pneumothorax.*

Before the advent of the more general use of the introduction of air into the pleural cavity as a therapeutic measure it appears that the term spontaneous or idiopathic pneumothorax was employed in a very limited sense by some authors. They used the term to designate the occurrence of air in the pleural space of individuals who previously had been apparently well and who, at the bedside examination, showed no pathological changes of the lungs or pleura. No fluid or pus accompanied the collapse and the lung returned to normal in a few weeks. These same authors used the term *secondary pneumothorax* to designate the occurrence of air in the pleural space of individuals who, at the bedside examination, showed various degrees of pathological change in the lungs or pleura. The pneumothorax under these conditions, in a large percentage of the cases, tended to persist permanently, or for a long period, and was usually accompanied by an accumulation of fluid or pus.

At the present time, both in the literature and in practice, pneumothorax is described either as *artificial* (therapeutic or induced) or *pontaneous* (natural). Artificial pneumothorax means the introduction of air into the pleural cavity for a definite purpose. Spontaneous pneumothorax means the occurrence of air in the pleural space other than when it is purposely injected. It is conceded to have a pathological basis with the possibility of very rare exceptions.

Spontaneous pneumothorax, as used in this sense, may occur from three general causes: (1) perforation of the chest wall and pleura from the

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outside, (2) perforation through the lung, bronchi or oesophagus, and (3) gases developing from existing effusions through the action of the *Bacillus aerogenes capsulatus*.

It is true that when there is a small amount of disease in the chest the occurrence of pneumothorax is rare. It is also true that when pneumothorax does occur under these conditions uncomplicated recovery in a few weeks is the rule. Inasmuch as these cases do not come to autopsy the demonstration of the pathological condition is rarely possible. At the present time the X-ray is helpful in clearing up these conditions. The ready recovery is the result of different factors. In the first place, as Fishberg (1) suggests, the tear in the visceral pleura most likely takes place over a part of the lung which is free from tubercles, with the result that the opening is small and closes early, and infection of the pleural space with the accumulation of fluid or pus does not take place. In the second place, owing to the small amount of disease present, there is little interference with the normal elasticity of the lungs, so that its expansion closely follows the early absorption of the air. The fact that these patients appear well and healthy after the pneumothorax has disappeared does not eliminate a pathological cause. It is well known that a fairly large proportion of persons have a considerable amount of disease in their lungs, especially tuberculosis, and yet remain feeling and looking apparently well. Musser (2) says, "pneumothorax may be the first symptom of tuberculosis." There have been reported about 66 cases of spontaneous pneumothorax occurring in persons previously healthy. Recovery has taken place in from one to ten weeks. Undoubtedly, many other cases have occurred which have not been reported or which have not been diagnosed.

With the more extensive diseases of the lungs the tear is very apt to open into the diseased area. The rent may be one inch or more in extent. Infection of the pneumothorax space is very liable. There are many cases, however, which have large pneumothorax pockets of long standing and an extensive disease of the lungs, and yet there is no fluid or pus present. In the patients with more extensive disease, in a large percentage of cases, the lung remains unexpanded. This is perhaps due to the patency of the original tear, loss of the lung elasticity due to the extensive disease, the presence of fluid or pus in the cavity when it occurs, thickened pleura, or to a combination of these factors. Rarely, even in the advanced cases, reëxpansion does take place in a few weeks. Recently, a case has come to my notice in which a large pocket occurred

as a result of spontaneous collapse of a lung with fairly extensive involvement. No complications followed and reëxpansion was complete in three weeks.

In McDonnell's discussion he employed the term spontaneous pneumothorax as though it were still used only in the former limited sense. His case appears to conform to this type as to onset and course, yet it occurred in a patient whose history, physical and X-ray findings, as given in the report, practically necessitate a diagnosis of pulmonary tuberculosis of long standing but of limited extent. The tearing of the lung by a pull of the old adhesion, as suggested by the X-ray, perhaps as a result of the extension of the arms while the patient was dressing, appears the most likely exciting cause in this case.

While it is possible to conceive of the occurrence of spontaneous pneumothorax in a perfectly healthy lung and pleura, it is doubtful whether it ever occurs other than as the result of a penetrating injury; as Babcock (3) brings out, an intraälveolar pressure, equal to from 100 to 300 cm. of water, is required to rupture the healthy lung.

In the more gross pathological conditions of the chest, in which spontaneous pneumothorax is a fairly common condition, tuberculosis seems to be the underlying cause of the greater percentage of the cases. Were it not for the extensive pleural adhesions that accompany these more extensive pathological conditions of the chest, spontaneous pneumothorax would no doubt be much more common, as a favorite site for the tuberculous foci is just beneath the pleural covering of the lung.

Morris (4), in a rather exhaustive review of the literature, finds that tuberculosis is reported to be the cause of spontaneous pneumothorax in from 30 to 90 per cent of the cases. In most of the reports studied the percentage was above 60. He quotes the following statistics from Biach which covers the study of the etiological factors in 918 causes of spontaneous pneumothorax: in this study 77.8 per cent were due to tuberculosis:

Phthisis	715	Perforation of stomach	2
Gangrene of the lung	65	Rupture of encapsulated peritoneal effusion	1
Empyema	45	Hydatid of lung	1
Injury	32	Caries of ribs	1
Bronchiectasis	10	Caries of sternum	1
Abscess of lung	10	Rupture of bronchial lymph nodes	1
Emphysema	7	Abscess of breast	1
Gangrene from infarction	4	Fistula between pleura and colon resulting from hydatids	1
Paracentesis, thoracic	3	Uncertain causes	4
Ascaris lumbricoides in pleural cavity	2		
Perforation of oesophagus	2		

Opinions differ greatly as to the frequency of spontaneous pneumothorax in tuberculosis. Morris in his studies found the figures to vary from 0.1 to 13 per cent. The character of the cases studied perhaps is a most important factor in this variation. Morris stated that the general average is 4.85 per cent, while the condition was found in only 2.64 per cent of their series of 636 cases of tuberculosis.

In my own experience spontaneous pneumothorax has been a relatively common occurrence. At present, in my service at the Los Angeles County Hospital, in one ward where I have 15 patients, all far advanced, there are 3 cases of spontaneous pneumothorax. In none of these is the collapse complete, although it is rather extensive in all. In every case the mediastinum appears fixed, so that there is very little, if any, collapse of the other lung. Dyspnea is present in only one of the cases. In this case there was considerable active trouble in the uncollapsed lung and there were two quarts of sterile serous fluid in the pneumothorax pocket. This fluid was replaced by air, resulting in some decrease in respiratory effort and a marked fall of temperature and pulse and considerable general improvement. There was no fluid present in the pneumothorax space of either of the other cases. One of these patients had a normal temperature and was very comfortable. His history indicated that he had received considerable benefit from the collapse. As far as could be ascertained, the collapse had occurred in all of these cases without their experiencing anything especially unusual. This may have been due, at least partly, to a rather low degree of intelligence on the part of all of these patients. They were all men, ranging in age from thirty-two to forty-two. The X-ray findings as reported in these cases were as follows:

W. S.: Right pneumothorax, lung collapsed except at base and apex where it is retained by adhesions. Large cavity in right apex; fluid level to the third interspace anteriorly; fibrosis and nodulation scattered throughout the left lung, most marked at the apex; typical tuberculosis.

H. M.: Disseminated tuberculosis of the right lung, considerable fibrosis with apical cavitation. Pneumothorax on the left side with complete collapse of the left lung except opposite the hilum; evidence of thickened pleura at the apex; costophrenic sulci obliterated on both sides by adhesions. This was the case in which temperature and pulse were normal and the patient rested comfortably in bed.

A. B.: Right lung, rather dense parenchymatous involvement throughout left lung, partial pneumothorax. Air-containing space above the fourth

rib with pleuritic bands and thickened parietal pleura; opacity at the left base continuous with the heart,—probably collapsed lung and thickened pleura,—heart displaced moderately to the left.

There are also at present three cases of spontaneous pneumothorax in my private practice. One is a complete collapse which occurred two years ago in a young woman twenty-seven years old. It occurred while the patient was sitting in a chair. The patient came under my care about three weeks later. The collapse was on the left side and the right border of the heart was in the right anterior axillary line. When seen, the patient had recovered from the first severe shock. There was some dyspnea and the pulse was rapid and irregular at times. There was very little involvement in the upper right lung. The patient was kept quietly in bed for four months, then allowed to get up gradually. During the fifth month after the onset the chest filled with fluid to the second rib anteriorly. The temperature during this time rose to about 99.6° in the afternoon and the pulse to 100. Interference, so as to ascertain the nature of the fluid or to aspirate, was repeatedly refused. At the end of a year the patient went home, where she did light housekeeping from June until January. She was seen occasionally. Her general condition was fairly good. Her pulse was always rather rapid. For periods of a week or more her temperature would be normal and it never went over 99.6°. The fluid remained at the same level. Two months ago she returned, saying that she had overdone during the holiday season and felt very nervous and tired. Her afternoon temperature was 99.6°, occasionally going to 100°. During the past week she consented to aspiration and three quarts of a thin, creamy tuberculous pus were removed. The cavity was washed out with normal saline solution, and two ounces of formaldehyde-glycerine solution injected and left in the cavity. During aspiration air was allowed to enter from the pneumothorax apparatus, so as to keep the pressure about neutral. At the end the air pressure was left slightly above neutral. The fluoroscope shows the left lung to be still entirely collapsed and the right border of the heart a little to the right of the midclavicular line on the right side. Since aspiration the patient's temperature and pulse have been normal and she feels much relieved. There is apparently no reaction, such as usually occurs from the formaldehyde-glycerine solution.

The second case is a young woman who came under my care in the sanatorium one year ago. The X-ray findings then were: right lung, peribronchial thickening with beading throughout; scattered parenchymatous involvement throughout to the third rib, most marked in the second interspace; left lung, spontaneous pneumothorax, with complete collapse of the lung from the apex to the fourth rib. There was no fluid in the pocket. There was peribronchial thickening of the descending bronchial trunk in the uncol-

lapsed portion of the lung. According to the patient's history, the pneumothorax had resulted in collapse of the area of most severe involvement. She has steadily improved and at present is free from symptoms and slightly above normal weight. She spends the day in the cure-chair, except for the afternoon rest hour and one hour during the day in walking. The collapse is still the same as when she entered the sanatorium. This patient has no recollection of when the collapse occurred. The mediastinum is not displaced, apparently being fixed by adhesions.

The third case is a young man with extensive fibroid involvement of long standing. He is up and around the greater part of the day. With the exception of a slight fever, considerable cough and expectoration and some dyspnea on exertion, he is fairly comfortable. He is not aware of when his pneumothorax occurred. The X-ray findings are as follows: right lung, scattered fibrosis through the upper lobe, and in the middle and lower lobes along the path of the bronchial trunks. Left lung, spontaneous pneumothorax with complete collapse of the lung above the clavicle; from the clavicle to the third rib the lung is collapsed in the outer half; there is also a small air pocket at the outer border opposite the fourth rib and in the costophrenic angle. The remainder of the lung is held by adhesions and shows a dense uniform opacity. There is no fluid present.

The rate of onset, the extent of the collapse, the degree of mobility of the mediastinum and the condition of the other lung, in most cases, determine the immediate symptoms of spontaneous pneumothorax, while the remote symptoms are dependent, as well, upon the associated conditions which may develop.

The treatment of spontaneous pneumothorax is symptomatic. As far as possible, interference should be avoided. In some cases there is a marked improvement in the patient's general condition following the occurrence of spontaneous pneumothorax. This is because the areas of greatest activity have been compressed and there is no severe infection of the pleural space, while there are sufficient adhesions to prevent marked displacement of the mediastinum with the resultant shock and mechanical difficulties. Kalb (5) states, "that as far back as 1837 it was noted that some cases of phthisis were arrested and a few were cured following spontaneous pneumothorax." In these cases that show improvement following the occurrence of pneumothorax, in which expansion tends to take place, compression should be maintained. This may be accomplished, to a certain extent, by fluid in those cases where it occurs. The method of preference is, however, by the introduction of air. This is possible only when the original opening has closed. If

fluid is present the air is introduced after aspiration. The objections to allowing the fluid to remain are: 1. Even when the fluid is reported sterile it may give rise to toxic symptoms. 2. It may give rise to pressure symptoms. These symptoms may be present when there is not more than a pint of fluid in the pleural cavity. At the same time fluid may fill the cavity, and this when the lung is almost entirely collapsed and the patient is not conscious of any marked symptoms due to its presence. 3. Infection of the fluid is very liable to take place. 4. When the fluid is present adhesions which tend to pull the lung out form more readily.

When the collapse of the lung is fairly complete and the mediastinum is not fixed by adhesions, so that its displacement with compression of the other lung gives rise to severe symptoms, as happens in the cases with valvular openings, repeated aspiration of the accumulated air affords marked relief. When the reaccumulation of the air takes place rapidly the insertion of a small cannula in the chest wall, which may be left for a period of days, may better serve the purpose.

When pyothorax supervenes and the original opening is closed, very satisfactory results in clearing up the infection in a large percentage of cases may be accomplished by repeated aspirations of the pus, followed by the injection of 2 per cent formaldehyde-glycerine solution. Injections of 95 per cent ethyl alcohol or up to 3 cc. of a saturated alcoholic solution of methylene blue have also been used effectively in these cases.

To recapitulate: I believe that we should endeavor to arrive at a common understanding as to what we mean by the term spontaneous pneumothorax; that spontaneous pneumothorax, as the term is more generally used at the present time, occurs with comparative frequency, especially in connection with pulmonary tuberculosis; and that, while it is a serious complication, its seriousness is nevertheless determined by the associated conditions and a certain small percentage of the cases are benefited.

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INTRATHORACIC MALIGNANT TUMOR SIMULATING TUBERCULOSIS

REPORT OF THREE CASES

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Case 1: In August, 1922, L. S., an automobile salesman, aged 29, presented himself for treatment, complaining of what he called pleurisy, at the base of the left lung, and of pains in the right hip and leg. There was some huskiness of voice and general weakness, associated with cough and expectoration.

Eight months previously (December, 1921) he had contracted a slight cold with which some bloodstreaked sputum was associated. Ten days later there developed a condition simulating lobar pneumonia in the left lower lobe, which kept him in bed for two weeks. At the end of January he was again at work, free from symptoms. On March 15 he felt extremely nervous, but had no pulmonary symptoms or fever. An X-ray of the chest, taken the next month, showed a marked, dense, opaque shadow at the left lung base, and a thoracentesis secured about 12 ounces of strawcolored fluid. The patient continued his work as salesman until June 1; then, following a picnic, he developed pain in the left chest (base) and shoulder, accompanied by a sudden rise of temperature to 103°, which subsided after severe purgation. This, in turn, was followed by a cough and the frequent occurrence of small hemoptyses and the expectoration of bloodclots. Huskiness of voice developed at this time, and became permanent.

Present Condition: A loss of 12 pounds in weight occurred within the last two months, and for the last six weeks the patient was in bed on account of weakness, pain in the right leg and hip, cough and expectoration, pain at the left base, and a daily afternoon temperature varying from 99.6° to 100°.

Physical Examination: Patient pale and poorly nourished, weighing 105 pounds, 14 below his normal average; temperature, 99°; blood Wassermann, negative; urine, negative; white blood cell count, 7800; red blood cell count, 5,000,000; hemoglobin, 76; non-protein nitrogen, 38.1; blood sugar, 80; alveolar CO_2 tension, 45; upper respiratory tract negative except for slightly enlarged tonsil; heart displaced to right, no murmurs; blood pressure, 120–90, soft, 90. Decreased expansion of left thorax; immobility of base with decreased reso-

nance over the lower two-thirds of left lung; apex beat visible within an inch of sternum; breath sounds distinct but not absent over area of decreased resonance, and feeble and rough over upper third of left thorax.

The *fluoroscope* showed a dense shadow occupying the lower two-thirds of the left thorax, the heart somewhat displaced to the right, and the left costophrenic angle and outline of the left cardiac border pushed to the right by what appeared as a dense mass in the lower two-thirds of the left lung. This shadow was opaque and of uniform density in its lower portion; but the upper border was irregular in outline, like a wave or cloud effect, sending undulations upward toward the outer clavicle and toward the upper lung root zone. This suggested a lymph node enlargement, such as is seen in cases of malignant tumor or Hodgkin's disease. A right-anterior-oblique plate showed that the whole posterior mediastinum was obliterated.

Thoracentesis was attempted and the needle, inserted in the seventh interspace, posterior axillary line, passed into a resistant mass. No fluid was obtained.

The *stereoroentgenogram* showed a peculiar dense shadow in the left thorax, which was rather characteristic of malignant tumor or Hodgkin's disease. The fact that the cervical lymph nodes were not involved and that there was no evidence of mediastinal enlargement to the right made the probability of malignant tumor the more likely.

On the assumption that this was a case of pulmonary malignant tumor, deep X-ray therapy was administered at intervals during eight weeks without bringing about any decided improvement in the patient's general condition or diminution of size or extent of the abnormality in the left lung. The patient slowly lost weight and strength; cough continued; some expectoration was present; and daily afternoon fever of 99° to 100° was noted. A few weeks later the patient died, when *autopsy* showed the growth in the left thorax to be a mediastinal spindle cell sarcoma.

The points in this case which simulated pulmonary tuberculosis are (1) age of patient, (2) continued afternoon fever of 99° to 100°, (3) loss of weight, (4) cough and expectoration, and (5) hemoptysis.

Case 2: On August 8, 1922, the patient, a man of 40, complained of cough, expectoration, slight dyspnea, loss of weight and dull pain in the right chest, with occasional radiation to the right shoulder. The cough had begun October, 1921, as a tickling sensation in the throat which did not respond to local treatments by a capable laryngologist. Later expectoration developed, and a distinct loss in weight (10 pounds) occurred. Anorexia and weakness were also in evidence.

The patient was poorly nourished, pale and weak; temperature, 98°; pulse, 90; weight, 131; blood pressure, 130–75; differential white blood count, normal (no eosinophilia); a few hyaline casts in urine; blood sugar, 100; alveolar CO_2 tension, 39.

The chest was slightly funnel-shaped; the right clavicle prominent; increased vocal fremitus over the back of the right lung close to the spine, opposite fourth to eighth dorsal spine; prolonged expiration below the right clavicle, with coarse râles, increased on coughing, in the back; whispered voice sounds as low as the sixth dorsal spine; below the left clavicle the breath sounds feeble as low as the fourth rib.

Stereoroentgenograms of the chest showed both lungs filled with irregular, smoke-like densities, typical of an advanced, active tuberculosis from an X-ray standpoint. Closer observation disclosed a few densities, round in outline, scattered throughout each lung and suggestive of tumor metastases. Right and left oblique films showed an obliteration of the normal view, due to the extensive lung root involvement.

On October 16 the patient died. *Autopsy* showed the presence of large dense areas of fibrosis infiltrated with medullary carcinoma. There was also extensive carcinomatous degeneration throughout the pleura and ribs.

The points in this case simulating tuberculosis were (1) history of cough and loss of weight, (2) the eliciting of coarse posttussal râles with prolonged expiration below the right clavicle, and (3) the X-ray evidence of generalized smoke-like, cottonwool density throughout the upper two-thirds of both lungs which is so typical of advanced tuberculosis.

Case 3: Mrs. H., aged 26, housewife, gave a history of uterine curettage a year ago; with this exception she had always been well until she developed a slight cough and, a week later, some bloodstreaked expectoration. On consulting a nose and throat specialist she was assured that her upper respiratory tract was normal, but on account of a daily afternoon fever was advised to have her chest examined.

An examination, made about five weeks after the initial cough, showed the following: weight 146 pounds, 14 pounds loss within six weeks; temperature, 100°; pulse, 90–100; asthmatic type of cough; bloodstreaked sputum, in which no acid-fast bacilli were found; blood Wassermann, negative; white blood count, normal; ***right lung***, harsh breathing and wheezing râles as low as the fourth rib in front and prolonged expiration in suprascapular region; ***left lung***, breath sounds very feeble as low as the fourth rib in front, and the same condition over the upper half in the back.

The *stereoroentgenograms* of the chest revealed in the right lung a peculiar dense bushy shadow protruding outward from the root zone; the outer border irregular; the whole density triangular in form, with apex extending outward into the middle vertical lung field. In the upper left lung there was a dense opaque shadow with a distinct clean-cut line of demarcation, suggesting a lobar pneumonia in formation.

The patient experienced the same clinical symptoms for the thirty days following this examination, except that the cough was looser and expectoration more plentiful, with further evidence of bright red blood mixed in the latter. The moist râles were now heard over the right lung root in front. The X-ray showed that the growth or density in this location had increased, the apex reaching the midaxillary line. On the thirty-third day the X-ray showed signs of softening of the density, either a resolution or a destructive process. On the thirty-fourth day, or almost the seventieth day after the appearance of the first symptom, the patient died suddenly of a severe pulmonary hemorrhage. Autopsy showed the growth to be a carcinoma (secondary).

The clinical data in this case which simulate pulmonary tuberculosis were (1) cough and expectoration developing without any definite upper respiratory disorder, (2) expectoration of bright red blood, (3) persistent afternoon fever of 99.1° to 100.2°, (4) the loss of about 16 pounds in weight, and (5) the prolonged expiration and râles in the upper pulmonary zones.

CONCLUSIONS

From these cases of pulmonary malignant tumor we may conclude that:

1. An afternoon fever of 99.2° to 100° and frank hemoptysis or blood-streaked sputum are frequently found in both pulmonary tuberculosis and malignant tumor, especially in young adults.

2. The physical signs in pulmonary malignant tumor are, as a rule, very indefinite as compared with the extent of the disease. Râles appear rather late.

3. The X-ray gives the most help in the diagnosis of pulmonary malignant tumor, and in most instances the only evidence on which to base a diagnosis. The shadows are often very characteristic.

THE RÔLE OF FORCED VIBRATIONS IN THE PRODUCTION OF PHYSICAL SIGNS[1, 2]

CHARLES M. MONTGOMERY[3]

This paper presents in outline a few of the principles concerned in forced vibrations and the application of these principles to the explanation of some of the physical signs encountered in pulmonary and pleural conditions.

In order to avoid lengthening the article unduly very little is said about the evidence on which many of its statements are based; that is, evidence derived first, from prominent physicists; second, from the literature; third, from animal experimentation, and fourth, from clinical data.

In the development of auscultatory phenomena between their place of initiation in the body and their reception by the stethoscope at the chest surface, three outstanding factors are recognized, namely, diffusion, reflection, and forced vibration.

The first two of these are simpler, more generally understood and, in many instances, more easily traceable than is the third.

Diffusion applies to that loss in intensity (energy) of sound waves that is due to dilution or dispersion consequent upon their spreading out through a progressively increasing space. In a medium in which the absorption is small enough to be neglected, and which is extended enough (infinite), so that the complications introduced by its boundaries may be disregarded, the intensity of a sound varies inversely as the square of its distance from the source. Typical examples are the reduction in intensity of the vocal resonance in suitable cases of pleural effusion, and the normal progressive loss in intensity of the vocal resonance as one moves the stethoscope downward from the lung over the liver.

The term *reflection* implies a forcing back of sound waves, that is, an obstruction with consequent diminution in intensity of these waves in

[1] Read by title before the American Climatological and Clinical Association, Niagara Falls, New York, May 24, 1923.

[2] Approved for publication by the Surgeon General, U.S.P.H.S.

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their regular forward progress. It is apt to be associated with a certain degree of absorption of sound, which then becomes transformed into some other sort of energy. The phenomenon is frequently met with in the chest where sound waves encounter changes in media of different density, for example, air and tissue or air and fluid. Examples are found in cases of pneumothorax with diminished vocal resonance, and in the normal lung, where the weakness or absence of the whispered sounds depends largely on reflection.

The same factor of reflection may also favor the transmission of sound waves under certain conditions; for example, through the speaking-tube effect of the trachea and bronchi, which carry waves deeply into the lung with a very considerable preservation of their energy by preventing diffusion.

Both diffusion and reflection, as here used, affect all sounds alike, whatever their pitch, as far as demonstrable evidence is available in the case of the chest, except in those cases in which a reflecting body, instead of reflecting, is set into forced vibration by encountering other vibrations of its own frequency. Diffusion and reflection, moreover, do not involve, as an integral part of their operation, the development or association of new sources of sounds.

Forced vibrations, on the other hand, are concerned especially with vibrations of limited ranges of pitch, and involve the development of new sources of sound, secondary to the primary or initiating source of the sound.

To clarify the subject at this point it may be well to mention three elements concerned in physical sound. The first is the sonorous or sound-producing body; for example, a tuning fork or the vocal cords set for speech. In the second place, we have the effects of such a vibrating sonorous body, which may be revealed as sound waves or as the setting into vibration of a new sonorous or sound-producing body, as exemplified by placing a vibrating tuning fork in contact with a suitable piece of wood. There is also a third element, namely, the force that sets a sonorous body into vibration; for example, the tapping of a tuning fork, the expiratory passage of air over the vocal cords in speech, or vibrations of a suitable pitch that excite forced vibrations.

Definition of forced vibrations: When a sonorous or sound-producing body, possessing a certain period or periods of vibration peculiar to itself, is set into vibration by external vibrations having its own, or somewhere near its own, natural period (periods) of vibration or frequency, it is said

to be forced into vibration by these external vibrations, that is, is set into forced vibration, and, under suitable circumstances, gives rise to a new sound. A sonorous body (like a suitable piece of wood) may be set into forced vibration first, by direct contact with another sonorous body of proper frequency of vibration (pitch), as when a wooden table is placed in contact with a vibrating tuning fork, or when the wood of a stringed instrument reinforces the string, the wood becoming an additional source of sound in both these cases. Secondly, a sonorous body may be set into forced vibration without any such direct contact with another sonorous body, but in response to sound waves of proper frequency; for example, when one tuning fork is set into vibration by another vibrating fork of similar frequency, but separated from it for some distance by air, in which case the sound waves in the air are the direct or immediately exciting cause of the vibration of the second fork, which itself then adds a new sound to that of the first fork.

A sonorous body then may give rise to sound in response to various exciting factors; for example, as commonly met with in percussing the chest, or as a result of encountering rhythmic vibrations of suitable frequency and sufficient energy.

Some sonorous bodies are set into vibration by other vibrations of only a very limited period or frequency of vibration. Thus, one tuning fork will respond to another of the same pitch, but ordinarily not at all to one of slightly different pitch. Other sonorous bodies, like the wood of a violin, respond to vibrations of many pitches coming from the strings, but even this wide capacity has its limitations.

The term *forced vibration* is herein employed to include a number of terms that are used more or less vaguely and with different meanings; for example, resonance and sympathetic vibrations.

It is important, in order to prevent confusion, to clearly differentiate between forced vibrations and simple sound waves, the former being capable of producing the latter, while the latter simply transmit the energy originated by sonorous bodies, that is, "conduct" the sound energy.

The rôle of forced vibrations in the explanation of physical signs: Inquiry into this subject naturally follows two lines. One is concerned with an analysis of sounds at their origin, especially as to their pitch and intensity. The other is concerned with the various structures or combinations of structures and materials between the original source of sound and the chest periphery, and seeks to determine to what extent these structures can be set into forced vibration, and what is their natural period or

frequency of vibration. Assuming that a sound of sufficient energy possesses a given pitch at its origin, and vibrations from this original source encounter media or structures of the same natural period of vibration, we would look, under proper conditions, for an amplification of sound from the new sonorous body that has responded with forced vibrations.

Analysis of sounds at their origin: An analysis of many of the sounds we are at present chiefly concerned in, namely, those originating in the upper respiratory tract during breathing, whispering and speaking (or singing), presents great and unfortunate difficulties, and for many of these sounds the subject is in a very incomplete state of development. Physicists have been concerned chiefly with the analysis of musical and so called rhythmical sounds.

It appears to be agreed by physicists today that most audible sounds are made up physically of one or more pure tones, that is, of individual sounds having a single vibration period, as exemplified in the case of the tuning fork. Sounds attributed to single pulses or waves, such as explosive sounds, will not be discussed here, having little if any known bearing on the subject in hand. No single unassociated sound is produced in the upper respiratory tract. The simplest form of sounds comes from the vocal cords during speech, but even these are composed of both fundamentals and overtones. All other sounds under consideration produced in the upper respiratory tract are much more complicated, consisting, presumably, of many individual sounds varying in pitch, intensity and duration. These complicated whole sounds still await complete analysis. They are produced in the upper respiratory tract during breathing and whispering. They also include all the sounds of speech except those produced by the vocal cords. In other words, the sounds made during speech by the lips, teeth, etc., and by the air escaping during expiration, fall into this very complex class.

Of prime importance is it to know the energy or intensity of the elemental sounds making up any complex sound. In the case of the vocal cords it is known that the original vibration energy is quite weak, but that this original energy is greatly added to (amplified) as a result of forced vibrations (resonance) set up in the chambers of the upper respiratory tract. In the case of the vocal cords the fundamental and overtone vibrations become greatly reinforced during speech. In the case of the other (non-vocal cord) sounds produced during speech, and in the case of the sounds produced in the upper respiratory tract during breathing

and whispering, we have some idea of what the total volume of sound is in each case, but we do not know the intensity of the individual tones composing each of these complex sounds. That these complex sounds are composed of many single tones finds clinical confirmation in the fact that they can be modified in quality and pitch by resonance or forced vibrations of many different pitches. Such multiplicity of sounds would indicate considerable weakness of each individual tone as compared to the total sound volume. Another evidence of feebleness of these individual tones is that even after being amplified by resonance or forced vibration they do not add much to the volume of the whole sound of which they form a part. The whole sounds produced in the upper respiratory tract during breathing and whispering become distinctly modified in other respects (quality and pitch) than intensity; for example, by the mouth and nasopharynx and also by bronchi and pathological cavities.

Our conception, then, of all these sounds, however loud, except those produced by the vocal cords, is that they are made up of individual tones that are much feebler than the whole sound. Such feeble sounds when amplified, whether ten or a hundred times, may still be relatively weak, and not add much to the original complex sound volume, though distinctly affecting its quality. Only the vocal cord vibrations reveal much amplification in the upper respiratory tract.

In the case of the bronchial tubes the natural vibration period of the contained air is of considerable frequency (high pitch) as far as it is clinically revealed, for example, over solid lung.

With suitable cavities communicating with bronchi the natural period of vibration varies in frequency, probably being usually greater than that of the normal lung or that of the fundamental vocal cord vibrations in the male.

The natural vibration period of a pneumothorax cavity is variable; apparently sometimes more frequent, rarely if ever much less frequent, than that of the normal lung tissue in a normal state of distention. The coin test gives a typical example of a resonance (forced vibration) phenomenon, the pneumothorax cavity apparently amplifying certain tones composing the sound produced by the coins.

The resonating chambers represented by bronchi and cavities do not ordinarily yield any great increase in sounds produced in the upper respiratory tract during breathing, whispering or speaking. All three classes of sounds receive some modification to yield a change in quality, the resonating chambers being set into forced vibration by single tones,

or combinations of a limited number of tones of closely corresponding frequency, these single or associated tones forming a small part of the whole sound coming from the upper respiratory tract. Thus, the breathing and whispered sounds over the trachea may become higher in pitch over a solid lung due to resonance (forced vibration) within the bronchi.

The normal lung gives us a particularly clear demonstration of the contribution of forced vibrations to physical signs, especially as revealed in normal vocal resonance. The natural vibration period of the normal lung is relatively slow (low pitch), and is revealed to a variable extent on percussing over normal chests, some chests yielding a more accurate determination than others. The pitch of this note very roughly corresponds to that of the normal vocal resonance and of normal vesicular inspiration.

Sounds failing because of unsuitable pitch to set the normal lung into forced vibration are actually obstructed by the normal lung in their attempted passage through it. This is largely because the tense membranes forming the alveolar walls interfere, through reflection, with the progress of the sound waves toward the chest surface.

The normal vocal resonance consists largely or wholly of sounds resulting from vibrations capable of setting into forced vibration the pulmonary tissues. Vibrations, to activate the lungs in this way, must possess sufficient energy and appropriate pitch. They are commonly found in the fundamental vocal cord vibrations amplified by the resonating chambers above the vocal cords.

The average man's voice yields good vocal resonance; but if it is sufficiently raised in pitch without change in intensity the vocal resonance can be made much weaker and like that in many women.

Other vibrations (pure tones) coming from the upper respiratory tract during speaking, and those produced during breathing and whispering, are believed not to come through to the chest surface unless in very feeble form, the reason apparently being that such vibrations are either of unsuitable pitch (too high) to give rise to forced vibration in the normal lung, or possess too little energy.

These same fundamental vocal cord vibrations appear also capable of setting into forced vibration the chest wall, probably chiefly the muscular tissue. Suitable percussion of the chest over the normal lung readily yields a sound which shows that it is a sonorous body and inferentially capable of yielding forced vibrations. This percussion note is often of a pitch close to that of the lung frequency and of the fundamen-

tal cord vibrations. Clinically, it is a striking fact that often deep pressure of the bell of a stethoscope yields much feebler vocal resonance than light pressure. The explanation appears to lie in the fact that firm pressure on the muscular tissue interferes with its capacity for being set into forced vibration. This muscular tissue differs from normal lung in that it does not interfere with the simple conduction of sound waves.

The normal vocal resonance, then, is believed to arise in the vibrations of the vocal cords, chiefly the lower pitched vibrations, these original vibrations setting into forced vibration, first, the resonating chambers above the vocal cords, this combined sound then setting into forced vibration the pulmonary tissue, and, finally, the muscular tissue of the chest wall also being set into forced vibration. Thus, three new sources of sound may be set into vibration in the production of normal vocal resonance. Vibrations of a sufficiently different pitch not only fail to excite these new sources of sound, but are actually impeded by the lung in their progress towards the surface.

It is believed also that these vocal cord vibrations are the only ones arising in the upper respiratory tract that yield audible sounds of any intensity over most of the normal chest under ordinary conditions.

The normal lung is not limited to a single period of vibration, though restricted within fairly narrow bounds. A person with a low pitched voice and good vocal resonance can distinctly increase the rate of the fundamental cord vibrations and still furnish a marked degree of vocal resonance.

The vibrations felt and heard over the chest during laughing and coughing are also traceable to vocal cord vibrations.

Abnormal fibrous tissue is believed likewise to be capable of producing sound under proper conditions, especially when it is both sufficiently attenuated and properly associated with air.

The acutely solidified lung presents a marked contrast in many physical manifestations to normal lung, notably in its acoustic properties. Such a lung no longer has the capacity of yielding forced vibrations, at least to any great extent. But instead of producing a new sound in response to suitable vibrations of a limited range of pitch of its own or nearly its own frequency, it has now become a relatively homogeneous medium, as far as sound waves are concerned, and transmits waves of different pitch equally well, with little loss of energy except that due to diffusion.

Over the solid lung we probably obtain sounds much the same as those within the bronchi connected with the solid lung, save for a change in intensity, and some change in quality due to the disappearance of the weaker vibrations. In other words, the sounds present in the upper respiratory tract during breathing, whispering and speaking appear in the bronchi somewhat altered in pitch and quality, largely due to forced vibrations set up in the bronchi, and then pass to the surface of the solid lung altered chiefly in intensity.

SUMMARY

It is believed that diffusion, reflection and forced vibration are the main factors in developing sounds between their origin in the upper respiratory tract and their arrival at the chest surface.

Forced vibrations are set up in a sonorous (sound-producing) body in response to the influence of vibrations of the same or somewhere near the same frequency.

A body set into forced vibration does more than simply conduct sound waves; it actually adds a new sound and thereby amplifies the original sound.

In order that external vibrations may set a sonorous body into forced vibration they must possess sufficient energy.

The sounds present in the upper respiratory tract during breathing, whispering and speaking are all complex or composite sounds, consisting of individual pure tones. The respiratory and whispered sounds present in the upper respiratory tract, also the sounds produced during speech, except those coming from the vocal cords, are probably composed of very many individual tones, varying in intensity but probably each one much weaker than the whole sound of which it is a part, and varying also in pitch and duration. The pure tones coming from the vocal cords are fewer and, after amplification in the upper respiratory tract, may have a relatively large amount of energy.

It is believed that the fundamental vocal cord vibrations, at least in the average adult male, are considerably lower in frequency (pitch) than all other, or most other, individual pure tones that go to make up the sounds present in the upper respiratory tract during breathing, whispering and speaking.

The development of the normal vocal resonance exemplifies well the effect of forced vibrations on physical signs. Initiated by the vocal cord vibrations, chiefly the lower pitched ones, the primary sound vibra-

tions become amplified through resonance (forced vibrations) in the upper respiratory tract, and pass down the bronchi into the pulmonary tissue, which is also set into forced vibration, and finally may set into vibration the muscular tissue of the chest wall. Other individual pure tones arising during speech, also the tones in the upper respiratory tract produced during breathing and whispering, are not sufficiently amplified anywhere to add much to the whole sound, because of deficient energy and unsuitable pitch; and, on reaching the normal lung, are actually obstructed in their passage and do not reach its surface or only in much attenuated degree.

The solid lung changes the picture. It has lost the forced vibration capacity of the normal lung and also its obstructive properties, becoming a good conductor for all sounds alike, so that the whisper, breathing and vocal resonance all come through and are much like those within the bronchi, except for loss in intensity. Vocal resonance (and particularly vocal fremitus) over solid lung (and over the back of the neck) may be actually less than over the normal lung, because forced vibrations are not possible in the acutely solid lung and nonsonorous neck. At the same time the whisper comes clearly through the solid lung and back of the neck because of the good conducting properties of both for all sounds. The whisper, however, fails to pass through the normal lung, being obstructed (largely through reflection) by it, and being unable to set it into forced vibration by reason of its too high pitch, as compared to that of the lung.

Individual tones going to make up the sounds produced in the upper respiratory tract (barring vocal cord sounds) are probably relatively weak compared to the whole sounds of which they are a part, and this is one reason why their intensity is not greatly appreciated at the chest surface, sufficient energy being lacking to set up forced vibrations. They do, however, set up forced vibrations of limited intensity in the bronchi and cavities, etc., sufficient to change the quality of the sounds audible at the chest surface, even if total intensity is not much affected.

Fibrous and other kinds of tissue in the lung, and also air, are capable of being set into forced vibration under conditions not mentioned.

THE INFLUENCE OF SILICA COMPOUNDS ON EXPERIMENTAL TUBERCULOSIS[1]

STUDIES ON THE BIOCHEMISTRY AND CHEMOTHERAPY OF TUBERCULOSIS. XXIX

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Silicates have been considered by a few clinicians and pharmacologists to exert a favorable influence in pulmonary tuberculosis, but on two entirely distinct grounds. One is based on the popular belief that persons who work at trades leading to the inhalation of certain silicious dusts are relatively free from pulmonary tuberculosis, presumably because the resulting pulmonary fibrosis helps to circumscribe and heal any existing tuberculous lesion (1). The same theory has been advanced concerning pulmonary anthracosis as a protective condition (2), and the reputed immunity of workers in lime dust has been attributed by some to a similar mechanical fibrosis, by others to hypercalcification of body fluids which is supposed to facilitate calcification and healing of tuberculous lesions. Landis (3) has reviewed the evidence on the effect of silicious dust on the lung, which seems to be conclusive that this is the form of pneumonokoniosis that leads to the greatest amount of injury to the pulmonary tissues, perhaps because of its gritty hardness. Coal dust seems to be best tolerated by the lungs, and plaster of Paris, clay and cement dust also produce much less injury than silica, quartz, flint, sandstone, emery and carborundum, as attested by the British Royal Commission on Metalliferous Mines and Quarries, and they lay particular emphasis on the harmfulness of fine crystalline silica as a cause of fibrosis.

This tendency to the production of pulmonary injury may, of course, be expected equally well to facilitate infection because of the tissue injury it produces, or to tend to healing by walling off tuberculous lesions. As a matter of evidence, however, this British Commission reported that there is "an excessive mortality from respiratory diseases,

[1] From the Otho S. A. Sprague Memorial Institute and the Department of Pathology, University of Chicago.

and especially from phthisis," from inhalation of dust of quartz, quartzite, flint and sandstone. Also, the granite workers of Vermont are reported as having an excessive tuberculosis rate (Hoffman). The difficulty with this statement, however, lies in the fact that the chalicosis itself leads to conditions which clinically resemble fibroid phthisis, and hence it is not certain that the reputed high incidence of tuberculosis in stone workers actually exists. Landis states that in his own experience this mistake has often been made, and that, when pulmonary tuberculosis does develop in persons with chalicosis, it commonly runs a chronic course, as Rössle (4) found for porcelain workers. Landis found, however, an actual high tuberculosis death rate in potters, which he attributes to the dust acting as a carrier of tubercle bacilli. Such attempts as have been reported in medical literature to secure curative effects through inhalation of inorganic dust, by tuberculosis patients or by infected animals, seem to have been unsuccessful.

Of most value are the studies of Gardner (5) who caused guinea pigs to inhale Vermont granite dust and also tubercle bacilli of low virulence. The strain of bacilli used, when inhaled alone, produces pulmonary tubercles which heal completely after a short time, but in animals inhaling both dust and bacilli the lesions are more numerous, larger, with an equal amount of caseation but more fibrosis, and persisting much longer than in the animals that did not receive dust. Cesa-Bianchi (6) also reported that guinea pigs subjected to dust inhalation were more susceptible to tubercle bacilli injected subcutaneously, which produced chiefly pulmonary lesions in these animals, while in the controls the lesions were especially in the spleen and liver.

Gye, Purdy and Kettle (7) point out that the insolubility of silica cannot well account for its extensive fibroplastic effect, especially since the more insoluble carbon dust has much less effect. Having found that dissolved colloidal silica is a strong tissue poison, they suggest that inhaled silica is slowly converted into this toxic colloidal form, and by injuring the tissues reduces local resistance to tubercle bacilli. The obstruction to lymphatics by the proliferated tissue may also prevent removal of tubercle bacilli from the lung in a normal way.

Although Gardner's experiments fail to show any evidence of a beneficial effect from the pulmonary fibrosis induced by the dust, and even indicate some decrease in local resistance, it cannot be said that they demonstrate what the effect of an old fibrosis in man may be on a newly acquired infection, or on the localization of existing latent infections,

or on the progress of human phthisis which differs from pulmonary tuberculosis in the guinea pig in that the human subject has more immunological defense against the bacilli.

An entirely different influence of silica in tuberculosis has been described by several German investigators, inspired largely by the pharmacologist, Kobert. One of his pupils, Siegfried (8), has reviewed the literature on silica up to 1901, discussing its importance as the chief constitutent of the earth, its distribution in the vegetable kingdom, and its occurrence in the animal body. Despite its insolubility, small amounts of silica are absorbed, chiefly from plant foods, so that minute traces are found in all the tissues and in the circulating blood. Especially large amounts are said to occur in the hair and feathers, but here the question inevitably arises as to the possibility of mechanical contamination of the external appendages with the omnipresent silicates. Against this assumption, however, is the statement that the hair of newborn infants contains nearly as much silica as that of adults (0.083 to 0.103 per cent of the ash), and it is present in the hen's egg and in the feathers of the unhatched chick. Furthermore, it seems to be particularly abundant in the Wharton's jelly of the umbilical cord. This would also indicate that silica circulates in so diffusible a form that it can pass from the mother to the fetus, a point of importance in considering its possible therapeutic utilization.

Apparently, connective tissue is especially rich in silica, and some authors ascribe to this element an important function in determining the elasticity and tensile strength of fibrous tissue, an idea which may well be doubted in view of the very small amounts of silica that are present.

In this laboratory Broman (9) has failed to find that feeding silica to rabbits with healing severed tendons leads to an appreciable increase in strength of the new formed connective tissue. Analysis of normal rabbits' tendons indicated the presence of 0.167 per cent of dry weight as silica, which is much more than was found by us in the normal tissues of guinea pigs, namely, lymph nodes 0.069, lungs 0.0196, liver 0.0062 and spleen 0.011 per cent.

Of the viscera, especially large amounts have been described in the pancreas,[2] which some have looked upon as the chief depository of silica for the body needs, analogous to the iodine storage of the thyroid.

[2] Lüning (Die anorganisch Bestandteile des Pankreas, Dissert., Würzburg, 1899) found in the ash of 2 human pancreases the following: SiO_2, 0.93 per cent; Ca, 16.94 per cent; Mg, 0.37 per cent.

In 1901 Hugo Schulz (10) also took up the study of tissue silica, and himself confirmed the statement that connective tissue is comparatively rich in silica, beef tendons having about 0.48 per cent of SiO_2 in the ash and spleen capsule 0.45 per cent, as compared with muscle, 0.08 per cent. In man corresponding results were obtained as follows, in per cent of SiO_2 in ash: muscle, 0.0531; skin, 0.1484; tendons, 0.3385; dura mater, 0.3361; fascia, 0.2462. He comments on the fact that silica seems related to the supporting structures in all forms of life, and suggests that this element may have therapeutic value in diseases in which the connective tissues are concerned.

According to the same author (11), young tissues contain more silica than old; for instance, tendons in the aged contain 0.0408 gm. SiO_2 per kilo, in young persons, 0.0865; muscle, 0.0191 as against 0.0257; skin, 0.0385 as compared to 0.0510. The umbilical cord he found to contain about 0.24 gm. of SiO_2 per kilo of dry substance[3] most of which can be extracted with hot water, although its form of combination was not determined. He found from 0.033 to 0.0400 gm. SiO_2 excreted in the urine per litre, the largest amounts when the diet consisted chiefly of beans and bran bread.

Presumably, the chief source of silica in the animal economy is from vegetable foods which contain much silica; and it is an interesting fact that numerous popular herb teas contain considerable soluble silica, and the same is true of certain mineral waters, some of which have had a reputation as of value in the treatment of phthisis. Zickgraf (12) ascribes to the silica content of a certain water an improvement in the character of the leucocytes in tuberculosis as indicated by the Arneth formula.

Kahle (13) undertook, in the pathological laboratory of Rössle at Jena, an investigation of the effect on experimental tuberculosis of an organic silica preparation devised by Dr. Weyland of the same university, the chemical nature of which is not disclosed. He found that in 3 cases of phthisis the amount of SiO_2 in the urine was low (0.007 to 0.0093 gm. per day), but as he says nothing concerning the diet these

[3] It may be suggested that the high figure for the SiO_2 content of the umbilical cord, reckoned on the dry weight of the cord, may depend, at least partly, on the relatively high water content of the Wharton's jelly, since the SiO_2 content may vary with the total weight of the fresh tissues. If the chloride content, for example, were reckoned on the basis of dry weight of tissue, the umbilical cord would also seem to be particularly rich in chlorides.

figures have little significance. Similar low figures were obtained in 5 cases of cancer. However, the statement is made that the scars of healed pulmonary lesions showed no more SiO_2 than normal connective tissues, but stress is laid on the reputed presence of silica in healed calcified tubercles. We have recently investigated the silica content of healed calcified human tuberculous lesions (14), and have found that they contain only such silica as may have reached the tissues from external sources through inhalation of dust. Calcified peribronchial lymph nodes and pulmonary lesions contain a small proportion of silica, but not more than uncalcified peribronchial lymph nodes or lung tissues contain in adults. This silica is derived chiefly, if not entirely, from inhaled silicious dust, for calcified tuberculous mesenteric lymph nodes do not contain appreciable amounts of silica, and only a trace was found in a calcified tuberculous pleural exudate. Therefore, these analyses furnish no chemical evidence supporting the hypothesis that silica plays an important part in the healing of tuberculous lesions. Calcified tuberculous lesions resemble in composition other calcified pathological tissues and also normal bone.

Kahle infected guinea pigs with large doses of tubercle bacilli, and gave them 0.5 to 2 gm. daily of Weyland's preparation in their food. He states that after only a few days' treatment there occurred a marked increase in the fibroplastic reaction in the tubercles, leading after a time to the formation of dense fibrous tissue. These changes were observed in tubercles in any and all tissues, in the liver there being a veritable cirrhosis. These anatomical observations are corroborated by Rössle, who says that it was possible to distinguish the tissues of the treated animals from those of untreated controls by their anatomical characteristics without other information. Rössle also comments (4) on his own observations on the resistance to tuberculous infection of porcelain and cement workers with pneumonokoniosis, but apparently found no evidence of anything more than a mechanical action of inhaled insoluble particles and the resulting pulmonary fibrosis. He also points out the significance of Kahle's observation that the SiO_2 content of the pancreas is high in cancer and low in tuberculosis, as related to the reputed lack of coexistence of these two diseases in the same person.

In 1921 Kahle (15) made a more extended report. He agrees with Schulz that the normal human pancreas contains about 0.14 to 0.15 gm. SiO_2 per kg. dry weight, and in 20 cases of tuberculosis found figures

ranging from 0.01 gm. in caseous pneumonia to 0.28 gm. per kg. of dry pancreas in healed tuberculosis, but in active tuberculosis the figures were usually much below normal. In pregnant women low figures were found, supposedly because of transfer of SiO_2 to the fetus, and possibly accounting for the susceptibility of pregnant women to tuberculosis; in a case of puerperal miliary tuberculosis he found no SiO_2 at all in the pancreas. However, in some cases of active tuberculosis he found high figures for SiO_2 in the pancreas. The finding of Schulz, that in tuberculosis there is no decrease in the pancreatic silica, Kahle attributes to a failure to differentiate between active and healed tuberculosis. He reports one experiment with a dog, in which the production of large wounds led to a decrease in the SiO_2 excreted in the urine, attributed to retention in the new-formed connective tissue; after the pancreas was resected the urinary SiO_2 was greatly increased. This experiment was not confirmed by repetition. He describes 20 experiments in the silica treatment (Weyland preparation) of guinea pigs infected with large doses of human tubercle bacilli, which caused a marked fibroplastic reaction about the lesions, although none of the animals was cured.

Gye and Kettle (16), who found that intravenous injections of colloidal silica leads to fibrosis in the liver and kidney, investigated its therapeutic value in animals. Rabbits were inoculated intravenously with human tubercle bacilli, in doses which were just sufficient to cause lesions visible to the naked eye two months after injection. Some of the animals were treated by mouth, or by intravenous injection, with soluble silica and an equal number left as controls. "In no instance was the process of tubercularization delayed or prevented by the silica; in a certain number of animals the process (*sic*) seemed to be helped by the drug, but in general it had no material effect on generalized tuberculosis." Thoma (17), in a similar series of experiments, found evidence that the colloidal silicic acid protected rabbits against infection by human tuberculosis; but if the animals were already infected there was no beneficial effect, and, if anything, the disease was more extensive in the treated animals. Clinical experience with the same preparation was equally unsatisfactory.

Kühn (18), collaborating with Kobert's laboratory in Rostock, reports that his clinical experience has indicated to him that administration of silica for long periods is beneficial in tuberculosis and also is of prophylactic value. For this purpose he has used a vegetable tea rich

in silica, and also tablets containing colloidal SiO_2, which he believes is utilized, since an increased urinary excretion of SiO_2 was observed after their administration, and also an increase in the blood.[4] He believes that coincident silica and calcium treatment cannot be accomplished because insoluble compounds are produced, but he recommends alternation of the two at considerable intervals. While admitting the absence of analyses for silica of lungs with and without tuberculosis, like Kobert he assumes the vital importance of silica for the healing of tuberculous lungs. He reports (19) that "a series" of guinea pigs were given injections of colloidal silicic acid (amount not stated) and infected with tuberculosis. Half of the silica-treated guinea pigs died in "some weeks" of pneumonia and showed no trace of tuberculosis; the remainder were alive after four months showing no trace of tuberculosis, while the control animals had died after 4 to 6 weeks with widespread tuberculosis. "Similar results" were obtained in a second series. Unfortunately, the lack of details makes it impossible to estimate the value of these experiments, but Kühn does not hesitate to state that they show that "guinea pigs may be immunized against tuberculosis with silicic acid injections." He reports having treated over 400 cases of tuberculosis with silica in various forms (silicic acid injections, *Silicol* tablets, herb teas) and considers the procedure beneficial in that the course of the disease is made more chronic, but he is very vague and indefinite, admitting that "*sichere Beweise stehen noch aus.*" As far as we can find, Kühn has not reported the eventual outcome of his animal experiments, and so we do not know whether or not they confirm Kahle's work on the influence of silica on fibrosis.

Much analytical work on silica in tissues, secretions and foods has been done in Kobert's laboratory by Gonnermann (20), who gives figures for the SiO_2 content of many human tissues, but does not include the pancreas, so that no comparison can be made bearing on the supposed importance of this organ as a silica reservoir. Neither does he discuss the relative richness in SiO_2 of normal and tuberculous tissues. We may also mention the analyses of Breest (21), who found that the bodies of mice fed silicates contained a little more than controls,—up to 5 mgm. in the entire body. (A review and repetition of this work will be found in the experimental part of this paper.)

[4] A discussion of the theory of silica absorption is given by S. Loewe (Klin. Wchnschr., 1922, i, 278).

Kesseler (22), like Kühn, treated patients with a vegetable silicium (43 to 272 mgm. SiO_2 per day), as well as calcium and silica tablets, and found an increase in the number of leucocytes, although not so striking an improvement in the Arneth formula as some others have described. He believes that he has seen clinical improvement "although the disease did not seem to us, as it did to Kühn, to exhibit under this therapy a course quite other than usually seen." In a case so treated that came to autopsy, however, he observed a marked connective tissue formation and encapsulation of the numerous pulmonary lesions.

Helwig (23) says that administration of SiO_2 to either men or animals causes a temporary fall in the number of leucocytes followed by a rise, especially of the polymorphonuclear forms, which show an exceptionally active phagocytic power. The Arneth formula is much improved, and in Helwig's opinion there is much clinical improvement even in advanced ulcerative pulmonary tuberculosis. Unfortunately, he gives no adequate details of either animal experiments or clinical observations.

Hayek (24) makes the following statement concerning silica therapy: "Not very pleasing are the very uncritical reports concerning the brilliant results from the 'tea cures' that have come from the clinical side. I myself have never been able to observe these startling results, although I have applied the silicic acid therapy very frequently in chronic consumptives." He goes on to say that he has tried subcutaneous injections of colloidal silicic acid (v. Heyden) in patients suffering for a long time with repeated small hemorrhages, and that, although the results observed so far were not convincing, they were enough to encourage further investigation.

To recapitulate, according to the authors cited:

(1) Inhalation of silicious dust leads to more fibrosis and to more untoward clinical effects than is the case with other forms of dust. Statistical evidence indicates that rough silica dust inhalation leads to a high tuberculosis death rate, but it is not certain that this statistical result may not be due in considerable measure to erroneous inclusion of non-tuberculous dust-produced pulmonary disease in the reported phthisis deaths. On the other hand, there are numerous statements in the literature to the effect that workers in some silicious dusts, for example, cement workers, are protected from tuberculosis. Animal experiments suggest the production of a lowered resistance to pulmonary tuberculosis from dust inhalation, but are inconclusive. If there is any beneficial effect from inhaled silicious dust it probably depends on fibrosis from

mechanical irritation, and not on any chemical action that can be used as a basis for therapeutics.

(2) On the basis of a limited and inadequate amount of analytical evidence, it is believed that connective tissues contain more silica than other tissues. Fom this it is assumed that silica is an essential constituent of connective tissue, but with no proof whatever. It is also assumed that administration of silicic acid or its compounds by mouth will increase the amount of connective tissue formed in response to tuberculous infection, and in this way will facilitate healing of the lesions and restriction of the progress of the infection.

In support of this hypothesis are advanced the following items:

(a) Low silica content has been described in the pancreas in a very small number of cases of active tuberculosis.

(b) Subnormal quantities of SiO_2 have been found in the urine in a very few cases of tuberculosis, but without any consideration of the silica intake or fecal excretion.

(c) Silica has been found in a few calcified nodules in lungs; but it has also been absent from others, and the lungs always contain silica from inhalation. Calcified tuberculous lymph nodes in sites not reached by inhaled silica have been found practically free from silica.

(d) Some clinical benefit has been attributed to the use of silicic acid in pulmonary tuberculosis, but all the published reports lack even the slightest evidence of control, and at the best the results described are very slight and vague.

(e) A few experimental animals treated with silicic acid are said to have outlived the controls, but not sufficient details of the experiments are furnished to support this statement.

(f) Tuberculous guinea pigs treated with a silicic acid compound are said to have shown a much greater connective tissue reaction about the lesions than the control animals. The details of this work have not been reported in a way that it can be critically considered, and it has not yet been confirmed by independent investigation.

The only justification for giving any consideration to the influence of silica on tuberculosis lies in the large amount of literature and uncritical work that already exist. There is no evidence submitted in favor of silica therapy that will stand the slightest criticism. The only significant item is the reputed increased fibroplastic reaction in tuberculous guinea pigs treated with silica, attested by a competent pathologist,

and largely on the strength of this we have undertaken a reinvestigation of the influence of silica on experimental tuberculosis in the guinea pig.

EXPERIMENTAL

On June 14, 1922, 40 guinea pigs were injected subcutaneously with a salt solution emulsion of virulent human tubercle bacilli (Dr. DeWitt's culture, no. 4015). Twenty of these animals were given 0.5 mgm., moist weight, tubercle bacilli. Ten of these were fed 1 gm. of *Silicol*[5] daily, except Sunday, from the day of inoculation. Ten were not fed silicol.

Twenty guinea pigs were given a smaller quantity, 0.1 mgm. of tubercle bacilli. Ten of these were fed 1 gm. silicol daily in the same manner. Ten were not fed silicol. As controls, 11 normal guinea pigs were fed 1 gm. of silicol daily. The silicol was fed in 2 gelatin capsules, each containing 0.5 gm., and was entirely supplementary to the regular laboratory diet of hay, oats and carrots. The guinea pigs inoculated weighed from 295 to 520 gm. with an average of 355 gm. The normal controls were somewhat heavier, weighing from 375 to 607 gm., with an average weight of 504 gm.

The tuberculous infection was allowed to run its course in the inoculated guinea pigs, whether the animal was fed silicol or not, except in the following cases: 3 animals were killed because of paralysis of the hind legs due to large open ulcers (caused by secondary infection at the site of inoculation). Two animals were killed two months after the other animals in their respective sets had died. One died of unknown cause seven days after injection; this animal is not included in the experiment.

As control material for chemical analysis and microscopic study, one normal silicol-fed guinea pig was killed for every 4 of the tuberculous animals.

At autopsy the lymph nodes, spleens, liver and lungs, all of which exhibited tuberculous lesions in the majority of cases, were removed, freed of excess blood by wiping and placed in 95 per cent alcohol until analyzed. Small portions of all tissues showing tuberculous involvement were saved for histological study. The ten livers of the animals of each series were analyzed together, likewise the ten lungs, spleens and the lymph nodes (intratracheal, parapan-

[5] This is described by the manufacturer (E. Laves, Lecinwerk, Hannover) as a SiO_2—casein—metaphosphate, containing about 25 per cent of SiO_2 in colloidal form. This preparation was selected as the one used by Kühn in some of his experiments. According to Zuckmayer, the silica administered in this preparation is absorbed in considerable amounts, and slowly excreted through the urine. An analysis of the preparation used in our experiments gave 26 per cent of SiO_2. The material is furnished in the form of a dry powder, readily administered in capsules. Theoretically, it is not broken up or absorbed until it reaches the intestines, thus avoiding the possibility of gastric irritation which is troublesome with some simpler silica compounds. We observed no harmful effects from feeding these comparatively enormous doses of silicol to guinea pigs.

creatic, inguinal and iliac) of each series were collected and analyzed. The tissues were removed from the alcohol, cut into small sections and dried at 110°. The liver tissue was extracted with ether for six hours in a soxhlet to avoid any error due to varying quantities of fat. The tissues were then ashed in new nickel crucibles, and the silica determined by the method of Lenher and Truog (25) with slight modifications adapted to smaller quantities of silica. The ash was removed to a platinum dish by means of a platinum spatula and dilute HCl. The mixture was evaporated to dryness on the steam bath. The ash was treated with 30 cc. of HCl (sp. gr. 1.07), and the mixture was evaporated to dryness. The residue was treated with HCl (sp. gr. 1.10), covered and heated on the steam bath for ten minutes. The solution was diluted with 5 cc. H_2O and filtered immediately. This filtration removes most of the silica. The filtrate was evaporated to dryness and dehydrated for two hours at 110°. This residue was taken up in 8 cc. HCl (sp. gr. 1.10), covered and heated on the steam bath for 5 minutes, diluted with 25 cc. H_2O, and filtered immediately. The dehydration was repeated if the amount of SiO_2 present on the last dehydration warranted the procedure. The two filter papers containing the SiO_2 were placed in a platinum crucible and ignited, ashed and weighed. The silica was determined by loss on volatilizing with hydrofluoric acid, after the addition of a few drops of dilute sulphuric acid. The amount of silica determined in the reagents used never exceeded 0.2 mgm. Control analyses of a pure SiO_2 preparation showed that the method was accurate for 0.5 mgm.

To check the results of the first experiment, on October 18, 1922, another series of 40 guinea pigs was inoculated in the same manner, 20 animals receiving the same larger injection and 20 animals receiving the smaller quantity of tubercle bacilli. Ten of each series were fed only 0.5 gm. silicol daily, instead of 1 gm. as in the first experiment. The inoculated animals weighed from 340 to 500 gm., with an average weight of 393 gm. The normal controls weighed from 360 to 490 gm., averaging 404 gm. There was no evidence of beneficial effect produced by the silicol treatment either in greater length of life of the treated animals or in the extent of the tuberculous involvement seen at autopsy. The silicol-fed pigs which had received the larger quantity of tubercle bacilli lived, on an average, 88 days, while their untreated controls lived on an average, 108 days. The silicol-fed animals which had received the smaller injection of tubercle bacilli lived, on an average, 124 days, while their untreated controls lived the same length of time. The amount and extent of tuberculosis grossly visible at autopsy was the same, as nearly as could be estimated, in treated and untreated animals.

ANATOMICAL STUDY

The degree of tuberculous involvement was estimated in the following manner: The four chief sites of tuberculosis were selected (lungs, spleen, liver and lymph nodes) and the extent of tuberculosis in each graded as follows: slight, 1; moderate, 2; marked, 3; extreme, 4. Hence, if an animal showed severe tuberculosis in all these four tissues it would be graded 16, the maximum. These gradings were added and averaged for the 40 that received silicol and the 39 that did not, the figures being 8.45 for the treated and 8.58 for the untreated. This difference is certainly within the limit of error for a method of such a limited exactness, and corroborates the impression gained by observation of the autopsied animals that there was no constant difference between the two sets of animals.

It was thought that the 1 gm. dose of silicol daily might be large enough to be toxic or irritating although no definite evidence of this was observed in the animals. A section of the small intestine of a normal silicol-fed guinea pig was studied microscopically, but no changes were found.

The influence of silica on the histological structure of the tuberculous lesion, and especially the amount of fibroplastic reaction, was determined in the following way: Sections were taken from the liver, spleen, lungs and lymph nodes of every animal used in these experiments, whether tuberculous, normal, silica-fed or not. Each section was then examined microscopically, with no knowledge on the part of the examiner as to whether the animal had received silicol, or how long it had survived infection. The grade of fibrosis in reaction to tuberculous infection was then estimated and recorded, graded for each organ as from 0 to 4+. After this had been done for all the tissues in all the animals, the total degree of fibroplastic reaction for each animal was estimated by considering the amount of involvement and amount of fibrosis, each animal being graded according to the following standard:

0—Little or no fibroplastic reaction, the tuberculous lesions everywhere showing merely necrosis with little or no fibrous tissue about them.

1+—Slight fibrous tissue formation about nearly all or all the lesions; this is generally most marked, if present, in the hepatic lesions, least in the spleen.

2+—Moderate fibrous reaction about all lesions, or slight about some and marked about others.

3+—Marked fibrous reaction about all lesions.

After this had been done in 71 animals, in which there were sufficiently extensively tuberculous lesions to make the results of value, the gradings were compared with the amount of silicol that had been fed. It was found that the ***amount of fibrosis thus objectively determined bore no relation whatever to the amount of silicol fed***, there being exactly as much fibrosis in the animals that received no silicol whatever. This is shown in the following summary:

GRADE OF FIBROSIS	NUMBER OF ANIMALS	NOT FED SILICOL	FED SILICOL
3	8	4	4
2	12	6	6
1	31	15	16
0	20	10	10
Total.....	71	35	36

It is seen that almost exactly the same number of silicol-fed and control animals exhibit each grade of fibrosis. Furthermore, in the animals fed silicol no difference exists in respect to fibrosis, whether the animals were given 0.5 or 1.0 gm. doses of silicol. It was also found that the amount of fibrosis was not determined in these animals by the size of the dose of tubercle bacilli with which the animals were injected.

These constant findings, we believe, completely refute the statement that the administration of silica to tuberculous guinea pigs increases the amount or character of fibrous tissue reaction. This varies greatly in different animals, why we do not know, but certainly it does not depend on the feeding of silicol.

CHEMICAL STUDY

Silica analyses were made of the lungs, lymph nodes, spleens and livers of normal guinea pigs. In order to have comparable weights of tissue for analysis, 31 spleens and the lymph nodes from as many animals were collected and analyzed. The lungs and livers were obtained from 10 normal guinea pigs. The tissues of each kind were united and analyzed as single lots, in order to secure enough silica to have figures of value (two or more milligrams). The results of these analyses are given in table 1, which shows that the lungs and lymph nodes contain much more silica than the liver and spleen. This may well be because each receives deposits of silicious dusts from outside the body.

The analytical figures for the silica content of the organs of normal guinea pigs fed silicol are shown in table 2. These indicate that silica feeding of normal animals leads to a definite increase in the amount of silica present in the liver and spleen, but not in the lungs. Inconstant results were obtained for the lymph nodes, presumably since when peribronchial nodes are included there are varying amounts of inhaled silicious dust present. Possibly the mesenteric nodes may contain more or less silicate absorbed directly from the intestines of animals fed large amounts of silica preparations.

TABLE 1

Silica content of organs of normal guinea pigs

	MGM. SiO_2 IN 100 GRAMS DRIED WEIGHT			
	Lungs	Lymph nodes	Livers	Spleens
	19.6	60.2	6.2	10.9

TABLE 2

Silica content of organs of normal guinea pigs fed silicol

NUMBER OF ANIMALS		AMOUNT SILICOL FED DAILY	AVERAGE NUMBER OF DAYS FED				
11		1 gm.	137	22.3	59.6	13.6	24.5
10		0.5 gm.	84	16.0	124.1	24.1	35.6
Average				19.15	91.8	18.8	30.05

TABLE 3

Silica content of organs of tuberculous guinea pigs fed silicol

	AMOUNT BACILLI INJECTED						
10	0.1 mgm.	1 gm.	124	20.5	118.7	0.2?	20.0
10	0.1 mgm.	0.5 gm.	71	13.7	54.3	11.3	5.3
10	0.5 mgm.	1 gm.	88	10.7	60.0	11.3	14.3
10	0.5 mgm.	0.5 gm.	63	8.0	35.0	8.2	4.5
Average				13.2	67.0		11.02

TABLE 4

Silica content of organs of tuberculous guinea pigs not fed silicol

10	0.1 mgm.		124	14.5	30.3	27.6	20.5
10	0.1 mgm.		87		25.4	21.9	12.2
9	0.5 mgm.		117	14.1	37.2	20.9	13.7
10	0.5 mgm.		87	18.3	47.5	14.1	4.5
Average				15.6	33.8	21.1	12.7

On the other hand, tables 3 and 4 show that feeding silicol to tuberculous pigs caused no increase in the quantity of silica present per 100 gm. dried weight of liver, spleen and lung. It is to be noted that the tuberculous organs of silica-fed guinea pigs show less silica than corresponding

organs in normal guinea pigs fed silica. This would suggest that such silica as is present is in the normal tissue, and the added cells and exudate of the tuberculous lesions, reduce the proportion of silica, since we find that the liver, lungs and spleen of tuberculous animals not fed silicol commonly contain as much or more silica than the tissues of tuberculous animals that were fed silicol. The occasional high figures in the lymph nodes are most probably explained by inhalation of excessive amounts of silica dust present in the cages of animals fed silicol. We found similar occasional excessive figures for calcium in the lymph nodes of animals fed calcium salts (14).

That normal peribronchial lymph nodes do ordinarily contain more silica than other lymph nodes is shown by the following observation: The lymph nodes from over 100 nontuberculous guinea pigs of various weights, killed in the laboratory in other experiments, were separated into two groups, (1) the peribronchial nodes and (2) all other nodes (mesenteric, inguinal and iliac), and the two lots were analyzed for silica. The results were:

	Per 100 gm. dried weight
Peribronchial lymph nodes	45 mgm. SiO_2
Other lymph nodes	28 mgm. SiO_2

A similar large series of actively tuberculous animals, not fed silicol, which had been killed in the course of another experiment in our laboratory, were studied in the same way with the following result:

	Per 100 gm. dried weight
Peribronchial lymph nodes	24.1 mgm. SiO_2
Other lymph nodes	26.4 mgm. SiO_2

If we compare these figures with those for the lymph nodes in tables 1 to 4 we find evidence that tuberculosis of the lymph nodes reduces the proportion of silica in the node, and that the excessively high figures for the lymph nodes in some of the animals fed silica probably depend on inhalation of silica dust from the fecal material in the cages. As no separation of the peribronchial from the other lymph nodes was made in the silicol-fed animals, it cannot be said definitely that the great increase in SiO_2 in the nodes of some groups of these guinea pigs was due to inhalation. Presumably the low silica figure for the lymph nodes of untreated tuberculous guinea pigs depends on the great increment of new tissue elements and exudate lowering the proportion of silica present in the original tissue.

Since the organs analyzed represented many different stages of tuberculous infection, an experiment was planned to determine whether the silica content varied with the progress of the disease. Spleens were classified as moderately tuberculous when they showed discrete active tubercles separated by normal tissue. The severely tuberculous spleens were almost entirely necrotic and usually very much enlarged, showing little, if any, normal tissue macroscopically. The results follow:

	Per 100 gm. dried tissue
Moderately tuberculous spleens	15.7 mgm.
Severely tuberculous spleens	9.0 mgm.

These figures support the assumption made previously that the more tuberculous change in a tissue the smaller the proportion of silica.

The pancreatic tissue from 41 tuberculous guinea pigs was analyzed for silica and also the pancreatic tissue from 31 normal guinea pigs, no silica having been fed in either group, with the following results:

	Per 100 gm. dried tissue, fat free
Normal pancreatic tissue of tuberculous guinea pigs	27.8 mgm.
Pancreatic tissue of normal guinea pigs	16.7 mgm.

The higher figure for the nontuberculous pancreas of actively tuberculous guinea pigs does not harmonize with the hypothesis of Kahle that the pancreas is a storehouse for silica which is depleted in active tuberculosis.

ABSORPTION OF SILICA BY MICE

In the introductory part of this paper (p. 324) reference was made to the work of Breest (21) whose experiment was performed as follows:

Nine mice, three months old, from two related strains, were fed 75 per cent wheat flour and sweetened condensed milk. After feeding 15 days, there was one day fast. He fed 75 mgm. SiO_2 in 15 daily 5 mgm. doses to one group, and to the other, 15 daily 6 milligram doses. Three were given colloidal silica hydrate, 3 sodium silicate, 2 neutralized silicate and only one was used as a control. Apparently, he analyzed the entire mice, hair, intestines and all. The control mouse had 0.15 per cent SiO_2 in its total ash, this being a total of 0.5 mgm. The other mice had from 0.19 to 1.22 per cent SiO_2. The highest figures were given by the mice fed the neutralized silicate. As these figures amounted to but 4.5 mgm. total silica retained, they represent but a very small proportion of the ingested silica. Actually, there was no appreciable increase in two of the mice, which had less than 1 mgm. SiO_2 in the ash. Nevertheless, Breest concluded that all these mice had absorbed and retained silica.

However, he also analyzed two untreated mice from another dealer and found in one 0.66 and in the other 2.72 per cent. He discussed, but did not explain the wide variations, including his own normal mouse with 0.15 per cent. He considered that, in view of his low figures with colloidal silicic acid, this was not absorbed. He gave no consideration to inhaled silica or silica in fur and intestine as a source of error. As a matter of fact, his figures do not at all establish his conclusion that silica had been absorbed, for this is based on comparison with a single mouse that gave a particularly low figure. Had he used as a basis the much higher figures which he found in two other normal mice the necessary conclusion would have been that feeding silica depletes the body silica. As a matter of fact the lack of adequate control makes the results valueless.

TABLE 5

GROUP	SKINNED BODIES OF THE MICE			SKIN, TAIL AND ALIMENTARY CANAL		
	Fresh weight (3 mice)	Weight of SiO_2 found	Per cent SiO_2	Fresh weight (3 mice)	Weight of SiO_2 found	Per cent SiO_2
Mice not fed silicol						
1	31.6736	0.0004	0.0012	12.9185	0.0025	0.019
2	29.0074	0.0005	0.0016	14.4165	0.0033	0.022
3	29.2720	0.0008	0.0027	13.0692	0.0009	0.0068
Mice fed silicol						
1	32.0713	0.0008	0.002	15.7484	0.0067	0.042
2	32.9484	0.0006	0.001	15.4012	0.0086	0.055

In order to study the question more fully the following experiment was performed:

Twelve mice were fed a diet consisting of two parts coarse yellow corn meal and one part whole milk powder (Dryco), to which had been added filter paper cut into small pieces for roughage. Twelve other mice were given the same diet, to which had been added 10 per cent silicol. One small carrot was given to each set daily.

At the end of twelve days 9 of the mice not fed the food with silicol were alive while 7 of those fed silicol lived. All food was removed from the cages on the evening of the twelfth day, and the mice were killed with illuminating gas the following morning. Their skins, tails and alimentary canals were collected and weighed separately, and then analyzed in groups of 3 each. The remaining skinned bodies, with the alimentary canal removed, were also weighed separately, and then analyzed in groups of 3, to determine how much silica had entered and been stored in the body as a result of silicol feeding. The results are given in table 5.

From these figures it is seen that feeding of silicol has not increased the amount of silica absorbed into the bodies of our 6 mice, the total amount in all being at the minimum quantity determinable even when three entire mice are used for each analysis. The skin and alimentary canal of normal mice contain much more silica than all the rest of the body. In animals fed silicol the skin and alimentary canal, removed twelve hours after feeding was stopped, contain more than twice as much as in the controls, probably part being in dust adherent to the hair and part silicol not yet eliminated from the intestines.

SUMMARY

A review of the literature on the use of silica preparations in the treatment of tuberculosis, human and experimental, leads to the conclusion that the evidence so far presented is far from establishing that beneficial results are obtained from the use of this element. On account of the large amount of conflicting or inadequately controlled testimony in respect to the effect of silica preparations on experimental tuberculosis, a reinvestigation of this subject has been carried out. It was found that administration of an organic silica preparation (*Silicol*, that is, SiO_2-casein-metaphosphate) to tuberculous guinea pigs does not increase the duration of life or modify the extent of tuberculous involvement of the tissues. Microscopic study showed absolutely no difference in the degree of fibroplastic reaction to tuberculous infection of the lungs, livers, spleens and lymph nodes in guinea pigs fed this silica preparation as compared with similarly infected animals not given silica treatment. Chemical examination of the entire bodies of mice fed silicol for twelve days showed no appreciable increase in the silica content in the entire body, from which the skin and intestine had been removed as contaminated with adherent but unabsorbed silica. Silicol feeding to normal guinea pigs led to an apparent increase in the amount of silica in the liver and spleen, and sometimes in the lymph nodes. Feeding of silicol to tuberculous guinea pigs caused no increase in the proportion of silica present in the tuberculous livers, spleens and lungs as compared with corresponding tuberculous organs in animals that were not fed silicol. Extensive tuberculous change in organs reduces the silica content below normal, whether the animals are fed silica or not, presumably because the exudative and new tissue elements reduce the proportion of silica. The pancreatic tissue of

tuberculous pigs contains more silica than the pancreas of nontuberculous guinea pigs, a finding which is not in harmony with the theory that the pancreas is a storehouse for silica which is depleted in active tuberculosis. The silica content of the lymph nodes of guinea pigs fed silicol is sometimes much higher than control animals, whether tuberculous or not, but usually there is no difference. These irregular figures probably depend on inhalation of silicious dust.

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THE INFLUENCE OF SILICA ON THE STRENGTH OF NEWLY FORMED CONNECTIVE TISSUE[1]

STUDIES ON THE BIOCHEMISTRY AND CHEMOTHERAPY OF TUBERCULOSIS. XXX

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Certain observers (1) having found that connective tissues contain somewhat more silica than other tissues, the hypothesis has been advanced that silica is an important factor in the tensile strength of connective tissue (2). Although the actual amount of silica present in connective tissue is so very small that this assumption may well be doubted, nevertheless it has served as the basis of a suggested method for the treatment of tuberculosis. Various silica-containing teas or drugs are being given with the hope of increasing the silica content of the tissues, and with the further hope that this will increase the amount and improve the quality of the connective tissue which forms the defensive reaction about the tuberculous lesions.[2] In order to learn whether the administration of silica actually does modify the strength of new formed connective tissues, a series of experiments was undertaken, following certain suggestions and technique found in an article by Lewis and Newcomer (3).

Their method was based upon a very early article by Paget (4). The object of their work was to study quantitatively the connective tissue factor in wound-healing. They found, however, that there was a wide variation in the tensile strength of connective tissue formed in response to surgical injury, and that there was no demonstrable relationship between the connective tissue repair following a routine surgical operation and natural resistance to inoculation tuberculosis in rabbits. They suggested the use of their method in the study of certain factors

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[2] An investigation of the influence of silica on experimental tuberculosis is published from this laboratory by Maver and Wells in the preceding article, AMERICAN REVIEW OF TUBERCULOSIS, 1923, viii, 318.

which might affect wound-healing, either through local or systemic application.

The method devised by Paget consisted in suspending weights to the Achilles tendon of a rabbit some days after operative division in order to learn the amount of tensile strength the new formed tissue possessed. Lewis and Newcomer carried out virtually the same procedure, using as the test weight a pail into which sand was run until the tendon broke.[3] Examination of the figures given by these authors leaves much question as to the quantitative value of the procedure, for great variations are found, ranging in one series of untreated animals from 4120 to 10600 gm., in another series from 4920 to 13750 gm. Therefore, the mere fact, that the averages of a large number of animals in two series are approximately the same, would seem to have little significance. Nevertheless, for lack of a better method, and particularly to test out this method, it was adopted with certain modifications to determine what effect, if any, the systemic administration of silica might have upon the healing of severed Achilles tendons.

PROCEDURE

The animals chosen were between one and two kilos in weight and of as near the same age as possible. They were fed once daily for five days two gram capsules of Silicol.[4] On the fifth day they were operated upon under light ether anesthesia. The region over the Achilles tendon was washed with green soap, shaved, and cleaned with alcohol. The tendon on both sides was severed cross-wise through a small longitudinal slit in the sheath. The tendon sheath and skin were closed with a single catgut stitch. Neither hemorrhage nor infection resulted. After the operation the silicol medication was continued for ten days more. The rabbit was then killed, the tendons were dissected free from the other structures and their tensile strength tested by a device similar to that used in testing the tensile strength of commercial catgut sutures, this being found to be more satisfactory than the weight method used by Lewis. One end of the tendon was fastened to a spring scale, the other, by means of copper wire, to a small drum upon which it could be slowly and steadily wound up until the tension on the tendon caused it to break. The reading on the scale was made by means of a stop gauge. In a few instances the tendon pulled out of the muscle without breaking. Such instances are

[3] A similar method has been used in a study of the strength of healing, sutured nerves by Miller (*Archives of Surgery*, 1921, lxxxviii, 167).

[4] Silicol is a commercial preparation described as SiO_2—casein—metaphosphate (E. Laves, Lecinwerk, Hannover) containing about 25 per cent of silica. It has been shown that silica is absorbed from the intestine when this preparation is fed.

recorded, however, because this material formed a part of the chemical analysis. The results are given in table 1.

TABLE 1

WEIGHT OF RABBIT AT BEGINNING OF EXPERIMENT	TENSILE STRENGTH OF RIGHT TENDO ACHILLES	TENSILE STRENGTH OF LEFT TENDO ACHILLES
grams		
1360	Broke at muscle margin	8744 gm.
1450	8541 gm.	7823 gm.
1530	6338 gm.	Broke at muscle margin
1670	Broke at muscle margin	Broke at muscle margin
1385	6328 gm.	7003 gm.
1350	7698 gm.	6638 gm.
2310	9300 gm.	6675 gm.
1040	7250 gm.	10120 gm.
2150	9875 gm.	7540 gm.
1920	8590 gm.	6720 gm.
1350	7600 gm.	2940 gm.
1644	10460 gm.	8522 gm.
Average 1596	8198 gm.	7272 gm.

It will be noted that there was a rather wide discrepancy between the tendons of the same rabbit, although the average strength of the two series differs by only a little over 10 per cent. Evidently these averages mean but little when there are such great variations between the two tendons of the same individual.

In order to control the results a series of normal animals, which had not been fed silicol, were operated upon and their tendons tested in an identical manner. The results were again very variable and are given in table 2.

TABLE 2

WEIGHT OF RABBIT AT BEGINNING OF EXPERIMENT	TENSILE STRENGTH OF RIGHT TENDO ACHILLES	TENSILE STRENGTH OF LEFT TENDO ACHILLES
grams		
1500	Broke at muscle margin	9810 gm.
1250	Broke at muscle margin	Broke at muscle margin
1580	9500 gm.	7850 gm.
2159	9545 gm.	12074 gm.
1818	10900 gm.	10450 gm.
2040	11800 gm.	11250 gm.
1800	10980 gm.	12150 gm.
Average 1735	10545 gm.	10594 gm.

Here the averages are close enough, but there are still wide variations between the two tendons from the same animal. The figures do show,

however, that repair of the tendons had not in ten days restored them to normal strength, for in three pairs of control rabbits the unoperated tendons did not break at all, the muscle separating from the tendon in long strands.

Chemical analyses were made by Miss Mary E. Maver of all tendon material to determine the percentage of silica present in normal rabbit tendons, that present in tendons ten days after operation in rabbits which had been given silicol, and in those which had not had silicol.

28 normal rabbit tendons yielded 0.167 per cent dry weight of silica.

24 operated, silicol-fed rabbits, 0.109 per cent dry weight of silica.

14 operated tendons, without silicol feeding, 0.079 per cent dry weight of silica.

Although the average tensile strength of the tendons from rabbits which had not been fed silicol was greater than that of those silicol-fed the percentage of silica found was less. In other words, the tendons which chemically contained the greater amount of silica had less tensile strength, and the tendons which had been operated upon, in both the silicol-fed and the non-silicol-fed, contained less silica than the normal tissue.

SUMMARY

No satisfactory conclusions can be drawn from these experiments, owing to the very wide natural variation in the tensile strength of healing, severed Achilles tendons. There was no correlation between the two tendons of the same animal, nor between the individuals of the series. Too many factors may be recognized as having a bearing upon the tensile strength of healing, severed tendons, to permit of any interpretation of the effect of medication upon those which are undergoing repair after surgical procedure, however painstakingly that procedure may be conducted. At least, it may be said that no direct relation was found to exist between silica content and tensile strength, and no evidence was obtained that silica administration in any way strengthened the healing tendon.

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THE AUTO-SERUM TEST FOR TUBERCULOSIS[1]

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In May, 1919, Wildbolz (1) described a test for active tuberculosis which has become known as the Wildbolz auto-urine test, for the detection of active tuberculosis in the human body.

Various other investigators have repeated his work with varying results, many of which are not conclusive. The majority of the published reports are unfavorable; a few, however, claim that the test parallels and, in some cases, excels the clinical findings.

Wildbolz's original work was performed on 200 cases, the majority of which were children. As a result, he claimed that a reaction never occurs unless the person gives a response of 1 to 10,000 tuberculin, and that the test is never positive unless there is an active focus of tuberculosis in the body. Anergic individuals were found to give negative reactions even when active tuberculosis could be demonstrated. Their urine was found to provoke a positive reaction, when applied to other allergic individuals, thereby rendering the test valuable in all cases.

Wildbolz uses the morning specimen of urine, evaporated *in vacuo* at 65 to 70°C. to one-tenth its original volume, and passed once or twice through a filter paper impregnated with 2 per cent phenol. He then makes three sets of injections on the arm, the upper two of which are with tuberculin diluted to 1 to 1000, while, 3 or 4 cm. below this, are made two more injections with a minute amount of the evaporated urine. The response in an active tuberculosis case is the same with the urine as with the diluted tuberculin, except that reaction from the latter persists longer than that from the former, which fades out completely after two or three days. No such response was obtained in nontuberculous cases, even in syphilis, influenza, etc. A urine containing staphylococci induced a nonspecific reaction, so that in certain cases of nephritis the findings are not pathognomonic. The specific nature of the urine antigen was demonstrated still more conclusively by the fact that an

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injection of 1 to 10,000 tuberculin, near the site of an apparently extinct urine reaction, frequently caused a flaring up of the latter.

In December, 1919, Miche (2) altered the technique. When the urine of the tuberculous suspect was now injected into a known allergic tuberculous individual, the findings paralleled the tuberculin control reaction in 17 positive cases and 4 negative cases, but in four cases they conflicted. Miche found the reaction more pronounced in the more active cases and weak in cases with favorable prognosis. He explains this on the ground that the urine was a tuberculin-antituberculin which was more potent in active cases.

Lanz (3) extended the Wildbolz test by applying the principle to whole blood as well as urine. His technique was to precipitate 10 cc. of whole blood with 20 volumes of 90 per cent alcohol. This was then evaporated *in vacuo* at 50 to 55°C. to its original volume and filtered through filter paper impregnated with 2 per cent phenol. Lanz believed the auto-serum test to be an improvement on the auto-urine test, in that one would not have to contend with the highly diluted antigens that occur in the urine of persons with impaired renal functions, nor with the variation in concentration of urines.

Imhof (4) repeated Lanz's work on 100 cases. His results, he claimed, were more reliable than clinical or X-ray findings. He found the auto-serum test superior to the auto-urine test in cases in which impaired kidney function prevented the elimination of antigens.

Gibson and Carroll (5) reported 40 cases. They concluded that the auto-urine test was of decided advantage in the differentiation between active and inactive tuberculosis, and preferable for children because of the greater ease in obtaining specimens. Bosch (6) reported similar favorable results on 220 cases.

Von Bergen (7) experimented on 400 cases. In attempting to determine the nature of the antigen, he demonstrated that the substance causing the reaction was not a protein but a thermostable, dialyzable, biuret-free, alcohol-soluble substance resembling tuberculin. He also noted that the urine should be evaporated in varying concentrations, in inverse proportion to the specific gravity. Favorable results were also reported by Schmid (8), Langraf (9), Stubbe (10) and others.

The foregoing investigators found the reaction more or less helpful. Others have not been so optimistic. Besançon and Weil (11), after a series of cases with controls, concluded (1) that the results were difficult to read, thereby introducing a personal factor; (2) that they were non-

specific, similar results being obtained in purulent interlobular pneumococcic pleurisy, catarrhal jaundice, gonorrheal rheumatism, aortic insufficiency, and after treatment with salicylates or valerian bases; and (3) that certain individuals react to any concentrated urine, normal or otherwise. In their opinion, the presence of antigens in the urine, while of possible scientific interest, is of no diagnostic or prognostic value. Others who found conflicting results were Farago and Randt (12), Kuhn (13), Levi (14), Orlianski (15), Schoenborn, Ottensmeyer and Potjan (16), Kušan (17) and Biese (18).

Kušan's work deserves special mention, for in a great variety of patients, he found the auto-urine test nonspecific and unreliable.

Our studies have been carried out at the Municipal Tuberculosis Sanitarium, City of Chicago, on more than 100 cases of tuberculosis in all stages and forms, from the far advanced pulmonary type to the nonactive lymph node cases, as well as on a few nontuberculous healthy individuals. The auto-serum test of Lanz was used with minor modifications by Carroll and Gibson, and ourselves. Our technique was as follows:

Preparation of serum: Ten cubic centimetres of blood, from an arm vein, is measured into an Erlenmeyer flask. To this is added slowly from a burette twenty times its volume of 90 per cent alcohol, the flask being shaken constantly. The first two volumes should be added at the rate of 60 to 75 drops per minute in order to form a fine powdery precipitate. The rest can be added more rapidly. This is allowed to stand in the icebox for twenty-four hours. It is then filtered through quantitative paper into a filter flask and the top of the flask is closed with a rubber stopper and a thermometer which have been freshly cleaned with alcohol, the thermometer being inserted through the stopper. The flask is attached to a suction pump and, when the temperature of the liquid is 10° to 14°C., the steam bath is placed underneath and evaporation is continued under reduced pressure until only the original volume of blood remains. This is filtered through quantitative paper, which has been previously folded, sterilized and moistened with 2 per cent phenol. The filtered serum should be clear or show only a slight cloudiness. Filtration is facilitated by using two or three filter papers, one placed on top of the other in the same funnel. Two tubes of bouillon are inoculated with the filtered serum and incubated for 24 or, better, 48 hours to test for sterility. The serum is sealed in small ampoules and kept in a cool place until used.

All glass ware must be thoroughly cleaned and sterilized before being used and extreme care must be taken to keep the serum sterile.

One drop of the serum is injected intracutaneously into the forearm of the patient. Within 24 to 48 hours a small papule, varying in size from that of a half-pea, which is barely discernible, to that of a large pea, which may be distinctly palpated, will occur in cases giving a positive reaction. A slight zone of redness may in some cases be seen extending from the point of injection to the surrounding tissue. No significance is attached to this, however, since a similar reaction may be observed in negative as well as positive cases. Imhof (4) stated that he examines for the reaction with closed eyes, disregarding in this way any redness or necrosis that might accompany a reaction to any foreign substance. A positive response is indicated entirely by an infiltration or palpable lump in the tissue at the point of injection.

RESULTS

Of 15 cases, far advanced and with positive sputums, 14 gave positive auto-serum reactions and one a negative. This case, *12,084*, is a young woman with positive sputum, yet in excellent physical condition. She has been working in the laboratory for more than a year. Her temperature is always normal and her physical findings are those of a healed lesion. She is a typical quiescent case. Two cases, *13,234* and *12,997*, giving very strong reactions, have both died since the tests were made.

Of 3 far advanced cases with negative sputum, 2 were positive and one negative. All 3 gave positive Pirquet reactions. The 2 cases giving positive auto-serum tests gave 3 complement-fixation tests for tuberculosis. Case *13,559*, giving a negative auto-serum test, has never had positive sputum and has since been discharged as an apparently arrested case. It is a question, therefore, whether this patient was tuberculous or had some other affection resembling tuberculosis clinically.

Of 8 moderately advanced cases with positive sputums, 7 were postive. Case *10,922* has had negative sputum for the last six months and is now apparently arrested. Case *10,803*, giving a marked reaction to the auto-serum test, is in fair physical condition but is subject to frequent hemorrhages and is quite active. All the others had definite activity.

Of the 21 moderately advanced cases with negative sputums, 14 were positive and 7 negative. Three of the negative cases, *13,863*, *12,462* and *11,663*, were apparently arrested at the time of the test. Cases *12,271*, *6,253*, *14,151* and *13,781* were all patients, in whom the physical findings at the time of the test were very slight if not negative, and all have since been discharged as apparently arrested. This was especially true in cases *12,271* and *13,781* who have been under close observation for

TABLE 1

Far advanced cases with positive sputum

CASE NUMBER	AGE	CLINICAL DIAGNOSIS	COMPLEMENT FIXATION		SPUTUM	PIRQUET	AUTO-SERUM	X-RAY FINDINGS
			Wassermann	Tuberculosis				
10980	20	Far advanced A	−	−	+		+	No X-ray
12432	18	Far advanced A	−	−	+	+	+	Excessive infiltration in right upper. Cavity in right upper
12084	21	Far advanced quiescent	−	−	+	+	−	Cavity in right apex. Excessive infiltration
13234	24	Far advanced B	−	−	+	+	++	Golden rod spray infiltration, both right and left
11427	17	Far advanced A	−	−	+	+	+	Bilateral lesion. Large cavity in upper left
11537	17	Far advanced A	−	−	+	+	+	Bilateral lesion. Cavities. Heavy consolidation in left side from apex to base
9028	17	Far advanced A	−	−	+	+	+	Dense extensive infiltration right upper lobe. Lower lobe less infiltration. Cavity under 4th rib
9027	17	Far advanced A	−	−	+	+	+	Infiltration throughout chest. Small cavity on upper right lobe. Multiple cavities in right upper lobe
9857	33	Far advanced A	−	−	+	+	+	No X-ray
10086	15	Far advanced A	−	++++	+	+	+	Upper left lung is dense, with heavy infiltration. Right side is network of cavities from apex to centre
10898	37	Far advanced A	−	−	+	+	+	No X-ray
13069	20	Far advanced A	−	−	+	+	+	Heavy infiltration on right, from apex to base. Multiple cavities. Light infiltration on left
12977	18	Far advanced A	−	−	+	+	++	No X-ray
10998	30	Far advanced A	−	++++	+	+	+	No X-ray
11302	26	Far advanced A	−	+++	+	+	+	No X-ray

TABLE 2

Far advanced cases with negative sputum

CASE NUMBER	AGE	CLINICAL DIAGNOSIS	COMPLEMENT FIXATION		SPUTUM	PIRQUET	AUTO-SERUM	X-RAY FINDINGS
			Wassermann	Tuberculosis				
13559	30	Far advanced A	−	−	−	+	−	No X-ray
5707	17	Far advanced A	+++	+++	−	+	+	Heavy infiltration from apex to base on left. Multiple cavities. Snowstorm appearance on right upper
11849	15	Far advanced A	−	+++	−	+	+	No X-ray

TABLE 3

Moderately advanced cases with positive sputum

CASE NUMBER	AGE	CLINICAL DIAGNOSIS	COMPLEMENT FIXATION		SPUTUM	PIRQUET	AUTO-SERUM	X-RAY FINDINGS
			Wassermann	Tuberculosis				
12050	20	Moderately advanced A	−	−	+	+	+	No X-ray
13631	17	Moderately advanced A	−	+	+	+	+	Heavy infiltration from apex to base. Multiple cavities on left and right. Infiltration from hilum
13194	22	Moderately advanced A	−	−	+	−	+	Heavy infiltration. Bilateral on upper part of chest. Multiple cavities
12514	33	Moderately advanced A	−	−	+	+	+	No X-ray
12436	18	Moderately advanced A	−	+++	+	+	+	No X-ray
10922	34	Moderately advanced A	−	−	+	+	−	Heavy infiltration on right. Cavity at 3rd rib. Light calcification on left
13384	30	Moderately advanced A	−	+	+	+	+	Heavy infiltration on both sides. Multiple cavities
10803	32	Moderately advanced A	−	−	+	+	++	Heavy infiltration in right upper. Multiple cavities on left side which has light snowstorm appearance

nearly a year. They are, to say the least, cases of questionable tuberculosis.

Of 24 incipient cases with negative sputums, 17 were positive and 7 negative. Of the 7 negative cases, 4 have since been diagnosed as nontuberculous. The other 3 have been discharged as apparently arrested.

Thirteen cases, diagnosed clinically as having lymph node tuberculosis, gave 9 positive and 4 negative reactions to the auto-serum test. These patients were mostly "contacts" and of the type of case in which the auto-serum test should be of greatest value. If it will pick out the active from the inactive contact cases, there is no limit to its value. One patient has never had any form of activity since entering the institution. A second is another preventorium patient with no signs of activity. She is fat, rosy and in the best of health. Two others have never shown any signs of disease. All the others have at the time, or since, been found to have some activity.

Up to this point the auto-serum test was found to parallel tuberculosis activity as closely as experimental methods permit. It may be due to the fact that only uncomplicated tuberculosis patients have been considered thus far. When we began to select patients that presented other complications the value of the test at once began to wane. For example, in table 7 the first two reactions were satisfactory, but in case *13,419*, one of an uncomplicated lung abscess, the test was strongly positive. In Mrs. E., a supposedly arrested case, it was positive. This, however, may have been more nearly correct than the clinical findings; but in cases 10,990, 5,866, 13,741, 13,947 and 13,675, with asthma, tachycardia or bronchiectasis the predominant ailment, all skin reactions were strongly positive. Some of these were classed as tuberculous by clinicians, but none were ever found positive on repeated search for tubercle bacilli. Furthermore, from our postmortem work we have found it a pretty safe rule to class this type of patient as nontuberculous. In such patients we have found syphilis, bronchiectasis, postinfluenzal pneumonitis, silicosis, etc., to be the cause of illness. To be sure, there are chronic fibroid tuberculosis patients who do give such findings, but there are points in the history and physical findings that will usually place them without much doubt.

Of the 8 cases, clinically nontuberculous, 7 were negative while one was positive. This individual has since been found clinically to have a healing lesion, with some activity at the time of the test.

TABLE 4

Moderately advanced cases with negative sputum

CASE NUMBER	AGE	CLINICAL DIAGNOSIS	COMPLEMENT FIXATION		SPUTUM	PIRQUET	AUTO-SERUM	X-RAY FINDINGS
			Wassermann	Tuberculosis				
11761	19	Moderately advanced A	−	+	−	+	+	Infiltration throughout entire chest. Honeycomb from clavicle to 6th rib on left. Thickened pleura 6th to 9th ribs
9767	19	Moderately advanced A	−	+	−	+	+	No X-ray
9662	33	Moderately advanced A	−	−	−	+	+	Apices are thick. Golden rod spray infiltration, from hilum to base
12656	17	Moderately advanced A	−	+	−	+	+	Density in lower part of chest. Infiltration extending from hilum to base. Apices clear
13437	26	Moderately advanced A	−	+	−	+	+	No X-ray
12145	32	Moderately advanced A	0	0	−	+	+	Infiltration from hilum to base. Right apex thick. Thickened pleura on left.
4950	31	Moderately advanced A	+	+++	−	+	+	No X-ray
12271	32	Moderately advanced A	−	−	−	+	−	Slight density at base of left lung. Apices clear
12890	25	Moderately advanced A	−	+++	−	+	+	Entire chest is hazy. Heavy infiltration from clavicle to base of both lungs. Small cavity in left lung.
13077	18	Moderately advanced A	−	+	−	+	+	Thickened bronchus on right. Light infiltration of lower half of left chest. Fan appearance from hilum
12452	37	Moderately advanced A	−	++	−	+	+	Calcified gland at hilum. Postinfluenza chest. Light infiltration at apices
9421	35	Moderately advanced A	−	−	−	+	+	No X-ray
13061	26	Moderately advanced A	−	+++	−	+	+	Accentuated hilum, right and left. Infiltration both sides from hilum to apex. Thickened pleura.

8757	23	Moderately advanced A	−	−	−	+	+	Postinfluenza. Accentuation of the hilum, both right and left
6253	33	Moderately advanced A	−	−	−	+	−	No X-ray
14151	27	Moderately advanced B	−	−	−	+	−	Right side hazy at 3rd to 4th ribs. Marked infiltration of golden rod spray left side from hilum to base
14284	7	Moderately advanced A	−	−	−	+	+	No X-ray
13781	31	Moderately advanced A	−	+	−	+	−	Right lung shows heavy infiltration from apex to base. Small cavity in left apex
12462	21	Moderately advanced A	−	+	−	+	−	Heavy infiltration on right side from hilum upward, covering entire apex. Small cavity between 5th and 6th ribs
11663	24	Moderately advanced A	−	+	+	+	−	Apices are clear. Light infiltration of golden rod spray from hilum to base, bilateral
13863	39	Moderately advanced A	−	+	−	+	−	Light infiltration from hilum to base. Apices clear

TABLE 5

Incipient cases with negative sputum

CASE NUMBER	AGE	CLINICAL DIAGNOSIS	COMPLEMENT FIXATION		SPUTUM	PIRQUET	AUTO-SERUM	X-RAY FINDINGS
			Wassermann	Tuberculosis				
13216	21	Incipient A	−	−	−	+	+	Marked infiltration from apex to base, bilateral. Thickened pleura on left
8183	38	Incipient A	−	−	−	+	+	No X-ray
13326	14	Incipient A	−	−	−	−	+	No X-ray
13632	32	Incipient A	−	+	−	+	+	No X-ray
13430	27	Incipient A	−	++	−	+	+	No X-ray
12153	16	Incipient A	−	++++	−	+	+	No X-ray
11208	16	Incipient A	−	++	−	+	+	Multiple calcified glands. Light infiltration of golden rod spray from hilum to apex and downward to base
12886	39	Incipient A	−	−	−	+	+	Postinfluenza. Bronchus thickened at base. Accentuated hilum with calcified glands
11737	30	Nontuberculous	−	++	−	+	−(?)	Apices clear. Postinfluenza chest
13548	18	Nontuberculous A later	−	−	−	+	+	Entire chest is hazy. Dense fan running from hilum to periphery and upward to clavicle
8459	21	Incipient A	−	−	−	+	+	Chest is hazy. Thickened pleura on left. Hilum accentuated. Calcified gland and hilum
12958	21	Incipient A	−	−	−	+	+	Apices thick. Golden rod spray infiltration on right to base
13890	16	Incipient A	−	++	−	+	+	No X-ray
13914	23	Nontuberculous	−	−	−	+	−	Chest is clear
13888	20	Incipient A	−	−	−	+	+	No X-ray
14005	24	Incipient A	−	−	−	+	+	No X-ray

13645	27	Incipient A	−	+	−	+	−	No X-ray
8632	35	Incipient A	−	−	−	+	+	No X-ray
11187	48	Incipient B	−	−	−	+	−	No X-ray
9687	32	Incipient B	−	−	−	+	+	No X-ray
13783	23	Incipient B	−	+	−	+	+	Heavy infiltration from apex to base, bilateral
12533	17	Nontuberculous	−	+	−	−	−	Left side is hazy. Golden rod spray from hilum to base and extending to apex on left
14004	31	Incipient B	−	++	−	+	−	Apices are clear. Mottled appearance of lower part of chest. Postinfluenza
12367	30	Incipient B	−	−	−	0	+	Chest is hazy. Hilum accentuated. Bilateral infiltration from hilum. Numerous calcified glands

TABLE 6

Lymph node cases

CASE NUMBER	AGE	CLINICAL DIAGNOSIS	COMPLEMENT FIXATION		SPUTUM	PIRQUET	AUTO-SERUM	X-RAY FINDINGS
			Wassermann	Tuberculosis				
13856	16	Lymph node tuberculosis	−	+	−	+	++	Heavy infiltration from apex to base. Bilateral
9166	13	Lymph node tuberculosis	−	+	−	−	−	No X-ray
11085	14	Lymph node tuberculosis	−	−	−	+	+	Light infiltration running from hilum to apex and to base, bilateral. Some calcified glands. Postinfluenza
13428	11	Lymph node tuberculosis Incipient A	−	0	−	+	+	Infiltration throughout chest
12169	14	Lymph node tuberculosis Incipient A	−	−	−	+	+	No X-ray
11165	12	Lymph node tuberculosis and pleurisy	−	−	−	+	+	Heavy accentuated golden rod spray extending from hilum to base and apex, bilateral. Thickened pleura
12383	9	Lymph node tuberculosis	0	0	−	+	−	No X-ray
13043	14	Lymph node tuberculosis	−	+++	−	+	+	No X-ray
9312	12	Lymph node tuberculosis	0	0	−	+	−	No X-ray
13262	13	Lymph node tuberculosis	−	−	−	+	+	No X-ray
13602	13	Lymph node tuberculosis	−	+	−	+	+	No X-ray
13505	8	Lymph node tuberculosis	−	++	−	−	−	No X-ray
14072	27	Lymph node tuberculosis	−	−	+	+	+	Heavy infiltration on right. Multiple cavities on right. Left side mottled

0=No test performed

TABLE 7

Miscellaneous cases

CASE NUMBER	AGE	CLINICAL DIAGNOSIS	COMPLEMENT FIXATION		SPUTUM	PIRQUET	AUTO-SERUM	X-RAY FINDINGS
			Wassermann	Tuberculosis				
12014	58	Lupus vulgaris	−	−	−		+	No X-ray
11798	38	Diagnosis conflicting. (Lupus erythematosus (?)	−	−	−	0	−	Postinfluenza chest. Apices clear
13419	15	Lung abscess	−	+	−	−	+	No X-ray
Mrs. E.		Arrested case. Has had active tuberculosis			−	+	+	No X-ray
10990	38	Tachycardia, with moderately advanced tuberculosis	−	−	−	+	+	Chest is hazy. Golden rod spray infiltration from hilum to base, and slightly upwards to apex
5866	52	Tachycardia with moderately advanced tuberculosis. Quiescent fibroid	−	−	−	+	+	No X-ray
13741	26	Asthma, with unquestionable tuberculosis	−	−	−	+	+	Infiltration throughout chest. Bilateral. More on right
13947	40	Asthma, with tuberculosis	−	++	−	+	+	No X-ray
13675	47	Bronchiectasis, with incipient tuberculosis	−	±	−	+	++	Heavy snow storm appearance throughout chest. Honeycomb appearance

TABLE 8

Nontuberculous cases

CASE NUMBER	AGE	CLINICAL DIAGNOSIS	COMPLEMENT FIXATION		SPUTUM	PIRQUET	AUTO-SERUM	X-RAY FINDINGS
			Wassermann	Tuberculosis				
A.J.H.	Young adults	Nontuberculous	−	+	−	+	−	No X-ray
C.L.		Nontuberculous	−	−	−	+	−	No X-ray
L.		Nontuberculous	−	−	−	−	−	No X-ray
E.R.		Nontuberculous	−	++	−	+	+	Healed tuberculosis from hilum to apex on right; slight amount of activity in axillary angle
C.J.H.		Nontuberculous	−	−	−	+	−	Chest is clear
Nurse (W)		Nontuberculous	−	−	−	+	−	No X-ray
Special 1		Nontuberculous	−	−	−	−	−	No X-ray
Special 2		Nontuberculous	−	−	−	−	−	No X-ray

DISCUSSION

One very interesting observation from these experiments is that a strong reaction seems to indicate a bad prognosis. This would show that the antigenic substance in the serum is either present in a higher concentration or that these cases have developed a greater degree of skin hypersensitiveness as a result of the disease. In either case, the result will be the same.

As regards the relation of this test with clinical findings, there were very few exceptions in which the test deviated from the clinical findings in cases in which the diagnosis is beyond question. Judgment of the test, therefore, should rest upon this type of case, rather than those in which there is some reasonable doubt as to the clinical diagnosis. For instance, in many types of lymph node cases, clinical men themselves differ. Therefore, if the auto-serum test can be proved accurate in unquestionable tuberculosis and can be proved to be dependable in unquestionable nontuberculous cases, it can be applied to the borderline or doubtful cases with confidence.

In this series there seems to be satisfactory parallelism between the clinical findings and the auto-serum reactions, particularly in differentiating activity from nonactivity; in helping to establish a prognosis; and in establishing activity in contact lymph node tuberculosis in children. One phase to be determined, however, is the rôle played by other diseases than tuberculosis. Besançon's (11) and Kušan's (17) work seems to indicate that other diseases respond to the test.

We have used the auto-serum in preference to the auto-urine test because of its aesthetic advantages, in the first place; second, because it does not produce necrosis; third, because it does not require adjustment of the concentration to the specific gravity as does the urine; and finally, it is more valuable in cases of retention where the antigens are held back from the urine. Furthermore, there is no reason to doubt that the concentration of waste products in urine is so great that it will elicit nonspecific reactions in hypersensitive individuals, whereas these same ingredients in the blood filtrate may not produce such nonspecific reactions.

The comparison of the complement-fixation test with the auto-serum test reveals a marked contrast. There were 21 positive complement-fixation tests out of 45 cases of frank tuberculosis, or 47 per cent, and 38 positive auto-serum tests, or 84 per cent. It is clear that the auto-

serum test, if proved reasonably specific, is far superior to any other laboratory method for the diagnosis of early tuberculosis.

The X-ray diagnoses, whenever possible, have been included; but, owing to the fact that not enough distinction was made between healed, healing, florid, lymph node or nontuberculous disease, they are not considered in the analysis. Few of the patients examined were considered nontuberculous from the X-ray standpoint. Negative results are always valuable, however; for when the chest was found "clear" the auto-serum test was always negative. For this reason, the X-ray is not considered to be the most important factor in diagnosis unless the finer points of the disease, mentioned above, are considered.

If we are to judge the work by that reported recently by Kušan (17) on the auto-urine test, we should be obliged to discard the whole procedure as worthless. It seems, however, that there are no grounds for such a pessimistic view. In the first place, the test is elicited by an antigen contained in the blood and not a heterogenous mixture of constituents that may be found in the urine. As it appears now, the antigen of tuberculosis seems to be far more active and acts in far smaller quantities than do other antigens. On this quantitative basis a rational test may be evolved. As an example, we may take a case of furunculosis or any other chronic infection produced by rapidly growing microörganisms. After preparing a vaccine from these, it requires millions of them to elicit the slightest response when injected into the skin of the host, while even a tenth of such a dose of tuberculin would produce a violent reaction or even death in a tuberculous subject.

It has also been suggested that, if this test is a tuberculin reaction, it should be equally as good to inject tuberculin instead of the concentrated serum. There are various explanations of why this need not be so. First, there is no way of gauging the dose of tuberculin so that it will be large enough to elicit a reaction and at the same time small enough not to overreact. There appears to be just the proper amount of this antigen liberated in active tuberculosis to produce a reaction in the cells that are being actively stimulated by the tuberculosis toxin. This antigen is also quantitative. The only problem yet to solve is whether other antigens produce a like response and, if they do, whether they can be diluted to leave the tuberculosis reaction in a group by itself.

We may take, as an example, the cases of tabes dorsalis cited by Kušan. The urine of such patients no doubt contains many toxic

metabolic products, that will elicit a reaction in the hypersensitive skin of a tabetic, yet it does not hold that that person's concentrated blood filtrate will cause such a reaction. It seems unlikely, because the toxin of syphilis is admitted to have a much lower potency than that of tuberculosis. It is reasonable to suppose, however, that there is a specific reaction due to syphilis, not only caused by the less powerful toxin but also due to the fact that the threshold of irritability of the cells has been raised not only to specific but also to nonspecific stimulation. This can only be eliminated by proper dilution, if at all. The same argument applies to other diseases, with the possible exception of the other chronic granulomata. They are not common enough, however, to cause serious interference with the results of this test.

The details of the procedure should be carried out precisely if good results are to be expected. The method of reading proposed by Imhoff is essential, that is, the reading of the papule should be made by palpation with closed eyes.

There still remains considerable work to be done before the true value of this reaction can be determined. So far, it seems to have some value when used in a restricted manner, but the nonspecific reactions are too numerous to permit of its widespread use, as it is performed at present.

SUMMARY

1. Wildbolz's auto-tuberculin test, as modified by Lanz, was applied to 100 individuals, most of whom were tuberculous; some were normal, while others had diseases other than tuberculosis.

2. Normal people gave uniformly negative reactions.

3. With few exceptions, active tuberculosis gave positive reactions.

4. Active lymph node "contact" patients gave positive results while inactive patients were negative. This, therefore, affords one of the most useful fields of usefulness for the test.

5. Certain diseases other than tuberculosis have been found to elicit the reaction, thus proving that, as used, it is not strictly specific for tuberculosis.

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SPECIFIC SERUM ANTIGENS IN TUBERCULOSIS[1]

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Since completing our study (1) on the auto-serum reaction of Lanz (2), a modification of Wildbolz's (3) auto-urine reaction, we have had the opportunity to test our former findings and make many additions to the previous lists. At the conclusion of our former work, there was fairly definite evidence that the test was positive in all active tuberculosis cases except possibly the terminal cases; that it was useful in picking out active "contact" cases in children; that normal individuals gave uniformly negative results; that a severe reaction indicated a bad prognosis; and that certain other conditions gave nonspecific reactions. We, therefore, continued this work in the hope that we might definitely settle the question of nonspecificity in the same manner that Besançon (4) and Kušan (5) have done for the auto-urine test; that we determine the relation between this reaction and clinical activity; that we might work out a method in sensitized animals to obviate nonspecificity; and, finally, that we might come to some definite conclusion as to the value of the test.

We have tabulated our former results in one table (table 1) and have attempted to compare the auto-serum results with clinical results. As will be readily appreciated, this is difficult to do without a common standard. Such common standards are the definite finding of tubercle bacilli and the definite finding of tuberculosis at autopsy. Less absolute standards are unmistakable physical signs, definite history (hemoptysis, contact, etc.) and X-ray evidence. In our former series there were 78 cases that we were not able to compare by absolute standards, that is, sputum was negative and no autopsies were performed. Seven of these were considered normal, and 15 were considered nontuberculous after a thorough re-check, leaving 56 cases with tuberculosis in which we were forced to depend for diagnosis upon these "relative" standards. The definite clinical signs and histories established the fact that most of these 56 patients were tuberculous. There

[1] From the Laboratories of the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

were from 5 to 7 cases, mostly in groups 4 and 5, however, as to which there was some doubt. Even if there were a few who were still nontuberculous, table 1 compares the clinical results with those of the auto-serum test in a rather crude but comprehensive manner.

According to this schema, the clinical diagnoses had an efficiency of 84 per cent, while the auto-serum test had an efficiency of 82 per cent. If the 5 or 7 cases, that were found positive clinically and negative by

TABLE 1

GROUP	NUMBER CASES	AGREEMENT	POSITIVE NEGATIVE DIAGNOSIS CLINICAL AUTO-SERUM	NEGATIVE POSITIVE DIAGNOSIS CLINICAL AUTO-SERUM	ERRONEOUS Omission	ERRONEOUS Commission	ERRONEOUS Omission	ERRONEOUS Commission	EFFICIENCY Clinical	EFFICIENCY Auto-serum	REMARKS
									per cent	*per cent*	
1. F. A. pos. sputum...	14	13	1	0	0	0	1	0	100	93	One case fibroid with some activity
2. F. A. neg. sputum...	3	2	1	0	0	1	0	0	66	100	Very probably nontuberculous
3. M.A. pos. sputum...	8	7	1	0	0	0	0	0	100	87	One found to be an arrested case
4. M.A. neg. sputum...	21	14	7	0	0	3	4	0	86	78	Nontuberculous (?)
5. Inc. neg. sputum....	24	17	7	0	0	4	3	0	83	88	Nontuberculous (?)
6. Gland cases.....	13	9	4	0	0	2	2	0	85	85	Contact cases. Continually negative.
7. Other diseases.....	9	7	0	2	0	5	0	7	44	22	
8. Normal controls.....	8	7	0	1	1	0	0	0	90	100	Considered as healed
Totals.....	100	76	21	3	1	15	10	7	84	82	

the auto-serum test, were definitely proved to be nontuberculous, then the auto-serum reaction would have an efficiency of 89 to 91, as against an efficiency of 77 to 79 for clinical methods. According to this analysis, clinicians have a tendency to err on the side of "commission" rather than "omission," while the auto-serum test, save in the nonspecific reactions, errs in the reverse manner. That is, the clinical diagnoses tend to include more conditions other than tuberculosis.

This takes into account only a few patients that have reacted nonspecifically. When the nonspecific groups are considered the value of the test sinks rapidly. As we shall see, the value of the test must be calculated without those chronic diseases that tend to cause a markedly

increased skin hypersensitiveness or an increase in some other antigen than tuberculin. In considering these groups, the mechanism of the reaction may profitably be considered, in an effort to determine whether it is anaphylaxis, a tuberculin reaction, a nonspecific chemical reaction or a reaction dependent upon skin hypersensitiveness in the suspect. Kušan (5) has shown that this hypersensitiveness plays a very large part in the reaction of the auto-urine test. The reaction is not exactly a tuberculin reaction because it disappears too rapidly. It may be due to a chemical irritation from an excess of metabolic products, assisted by an extremely dilute tuberculin, one that is too dilute to persist as long as the regular reaction. There is still the possibility of some anaphylactic properties to this reaction. As Zinnser (6) has shown with tuberculin, it may be a combination of a tuberculin and an anaphylactic reaction. The other two factors may also play varying rôles, depending on the disease complication and skin condition present.

In uncomplicated tuberculosis there appears to be a rather uniform type of reaction that is different from the ordinary tuberculin reaction. Imhoff (7) has pointed this out, and we have found that his suggestions must be followed if any dependence is to be placed on the test. An erythema, or necrosis due to the alcohol in the evaporate, must be ignored and *only a definite shot-like papule must be considered.* It is better to read the reaction blindfolded. This we did during the latter part of our experiments. The identity of the patient was kept from the examiner. Only the papule was considered as positive. This reason alone is enough to explain the variegated results obtained by different observers. From the lack of erythema, the reaction would appear to be caused by a vasoconstriction with edema, rather than by a vasodilatation and infiltration. In this respect it is more of the nature of a urticarial reaction than tuberculin reaction. This effect on the vessel walls would make one think of an anaphylactic process in the early phase of the reaction or the first phase of a tuberculin reaction, according to Zinnser. When the reaction is marked and the second phase of the tuberculin reaction (or the true tuberculin reaction) begins to appear it indicates a more concentrated auto-tuberculin and a bad prognosis.

As the different groups are considered, the clinical and auto-serum results appear to harmonize fairly well until group 7 is reached. Here the first diagnoses check fairly well but on a more careful examination most of the patients of this group were placed in the nontuberculous class.

The auto-serum reaction is, therefore, not dependable in these patients. It was no worse, however, than the preliminary clinical diagnoses in this type, and was also equal to them in ruling out inactive tuberculosis and other diseases simulating early tuberculosis.

In order to check more completely this nonspecificity we selected a few random patients, for whom we were able to apply the absolute standards mentioned above. In one patient, R. S., who had an Addisonian syndrome with a questionable Hodgkin's disease, there was a definitely positive reaction which receded only a trifle earlier than the ordinary reaction. At autopsy there was found an uncomplicated Hodgkin's disease, with glandular hypertrophy in the region of the adrenals, and no tuberculosis. Another patient with a four plus Wassermann reaction also gave a positive reaction. This patient cleared up rapidly on antisyphilitic treatment. Two other syphilitics, however, (presumably earlier cases), gave negative reactions. One other patient, having a marked pleural thickening and "postinfluenzal pneumonitis," with no evidence of tuberculosis at autopsy, gave a positive reaction. These findings, taken with those in the earlier work, prove that this reaction may be elicited by other antigens than those of tuberculosis. Seventeen other tests were performed, however, when the clinical and laboratory signs were absolute for tuberculosis. In every instance there was agreement.

The next series of experiments were performed on animals in an attempt to rule out this nonspecific phase, by sensitizing the animal (guinea pig) to tuberculosis, and in four weeks shaving their bellies and performing the injections in the usual manner. The results were wholly negative, as were Kušan's with the auto-urine test. The alcohol in the evaporate caused a local necrosis, but there was no papule at any time and normal animals gave the same type of reaction as the tuberculous.

After satisfying ourselves that the nonspecific phase of the reaction deprived it of most of its useful potentialities and that this nonspecific phase could not be ruled out by the use of sensitized animals, we made a final attempt to salvage the test, trying to determine whether there is any sharp line of demarcation between the active and the inactive stages in the same patient. In this we were partially successful. The results are tabulated in table 2.

Patient S. L. had a pyocyaneous infection on an old influenza pneumonia, with only a slight tuberculous involvement. Her sputum was

positive a very few times. She was persistently negative to the auto-serum test, but strongly positive to the Pirquet.

TABLE 2

Auto-serum tests before and after sanatorium treatment

PATIENT	SPUTUM		CLINICAL CONDITION AT FIRST TEST	CLINICAL CONDITION AT SECOND TEST	RESULTS OF FIRST TEST			RESULTS OF SECOND TEST		
	First test	Second test			Auto-serum	Tuberculin 1 to 1000	Tuberculin 1 to 10,000	Auto-serum	Tuberculin 1 to 1000	Tuberculin 1 to 10,000
S.L. 11663	+*	−	Inc. B. with bronchiectasis	Arrested T.B. Working half time	−	+	+	−	++	+
D.C. 13429	+	−	Much activity. M.A.B.	Slight activity. M.A.A. Working three-fourth time	+	+	+	+	+	+
F.K. 12906	+	−	Much activity. F.A.B.	Slight activity. F.A.A.	+	++	+	∓	++	+
F.K. 9662	+	−	Slight activity. M.A.B.	Arrested. Working full time	+	+	+	−	+	−
H.L. 11208	+	−	Slight activity. M.A.B.	Arrested. Working full time	+	+	−	−	+	−
F.B.	−	−	Slight activity. M.A.B.	Arrested	+	+	−	−	+	−
L.H.	−		Arrested. Working full time F.A.B.		−	++	+			
E.	−	−	Arrested. Inc.B.	Arrested. Working full time	+	+	−	−	+	−
A.P.	−	−	Activity. Inc.B.	Arrested. Discharged. Working	+	+	−	+	+	−
M.I.L.	−		Quiescent. Fibroid		+	++	+			
R.S. 16610	−		Advanced Hodgkin's disease		+	+	−			
R.C.B.	−		Normal man with no signs of tuberculosis		−	++	∓			
L.A.	−		Normal man with no signs of tuberculosis		∓	++	∓			

* Animal inoculation.

Patient D. C. had considerable activity on the repeated test as well as on the first. She was continually positive. Patient Fr. Ken. was very active on the first test but only slightly so on the repeated test.

Her skin reaction was likewise less marked on the second test. Fr. Kad., H. L., F. B. and Mrs. E. were completely arrested on the repeated tests and the skin reactions were negative. Mrs. E. gave a positive reaction on the first test after the clinicians pronounced her negative. L. H. was an ex-patient, arrested for three years, who gave a negative skin reaction. A. P., although working for some time after a supposed arrest, still gave a positive skin reaction. M. I. L. was an old arrested fibroid of five and more years duration who gave a strongly positive skin reaction. R. S. was an uncomplicated Hodgkin's disease who gave a mild reaction. R. C. B. a normal man was negative. L. A., a rather robust, supposedly normal man, gave a doubtful reaction. There were no signs of activity to be found in this last instance.

While the skin reaction was a decided failure in a few of this last series, there were many instances when it parallelled the tuberculous activity very closely.

DISCUSSION AND CONCLUSIONS

After a rather brief but comprehensive study on the auto-serum reaction of Wildbolz, as modified by Lanz, we have come to the conclusion that, although there is a definite and rather large field for its usefulness, it nevertheless falls short of being the test its authors originally claimed it to be. The reaction may be elicited by other antigens present in the body, especially in lung abscess, bronchiectasis, chronic syphilis, Hodgkin's disease, etc. There is no doubt a factor of skin hypersensitiveness present in all chronic toxemias that helps to give the reaction. There may be a partial effect of a nonspecific chemical reaction and also of a slight tuberculin reaction in the response. Although there is no doubt a variable play of these factors, the greater part of the true reaction seems to be similar to a localized anaphylaxis, causing an edema with little cellular infiltration, followed in the more severe types of reaction by what Zinnser has described as the second stage of the tuberculin reaction, produced by infection only and by proteose-like bodies from living tubercle bacilli.

These findings have definitely narrowed the usefulness of the test to the differentiation of activity in contact and lymph node cases in children before clinical or X-ray signs appear, to determine when to discharge a known tuberculous individual from a sanatorium, and to prognosticate in certain far advanced patients, for a severe reac-

tion was found to indicate a bad prognosis. In spite of the fact that the nonspecific element depreciates the value of the test, we still feel that the above mentioned reasons are enough to justify its use.

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THE WILDBOLZ AUTO-URINE REACTION IN TUBERCULOSIS[1]

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At present, the only means at our disposal for the determination of the activity of tuberculosis is a careful inquiry into the symptoms of toxemia and a close observation of the temperature and pulse rate over a period of time. Unfortunately, when the patient is quiet and resting the symptoms of toxemia may disappear, only to reappear again at the slightest exertion. Then again, the symptoms of toxemia may occur with any disease. We often attribute to a healed tuberculosis the symptoms that occur with some other concurrent infection, as, for example, infected tonsils, teeth, sinuses, etc.

Any test, whatever it may be, must not only determine the activity of tuberculosis but must also be specific for the disease itself. Many investigations have been made for such a test. The tuberculin and complement-fixation reactions and the X-ray have been advocated as means for diagnosing activity. Though they all have many supporters, the success of any one of them has not been striking enough to be adopted as a specific test.

When Wildbolz (1) published his account of the *Autourine Reaction* considerable interest was aroused because in it we had both a test for activity and diagnosis of the disease. His work was based on the fact that products of elimination and disintegration of the tubercle bacilli are present in the blood and excreted through into the urine. He therefore concentrated the urine until these products of elimination and disintegration were in sufficient quantity to produce a reaction when injected intracutaneously into the same patient or one known to give a reaction on being injected with a 1 to 10,000 dilution of old tuberculin. The reaction was similar to the specific reaction produced by O. T.

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Since the publication of this test of activity, many have repeated Wildbolz's work. However, their results and conclusions are not uniform as the following review indicates:

Imhoff (2) of Wildbolz's clinic obtained the same results as Wildbolz, except for 10 per cent of nonspecific reactions, which he thought might have been due to the urinary salts. Lanz (3) thought the reaction to be specific. He warned against immediate reactions that are not specific and are due to salts. To avoid the nonspecific reaction he gave a method of dialysis to get rid of the salts. Schmid (4), basing his conclusions on 150 cases of pulmonary and surgical tuberculosis, believed the reaction to be specific. Boenighaus (5) reported positive reactions in 75 per cent of tuberculous cases and in 12.5 per cent of nontuberculous cases. He also reported 80 per cent positive cases in pregnant women. He concluded that the reaction may be specific but in its present form it is not decisive. Landgraf (6) tested 100 cases, and reported positive results in 90 per cent of cases of open pulmonary tuberculosis, in 80 per cent of closed pulmonary tuberculosis and 44 per cent of doubtful cases. He further stated that in cases of lung lesions other than tuberculosis negative results were obtained. Offenbacher (7) did not believe the urine to be specific. Farago and Randt (8) concluded that the reactions obtained were due to chemical constituents in the urine. Orlianski (9) stated that it cannot be determined whether the reactions are due to the specific substances found only in the urine of the actively tuberculous, or to the nonspecific albumoses which are frequently found in tuberculous patients with fever, or to the richer salt content of morning urine after night sweats. Levi (10), experimenting with 12 healthy individuals, obtained reactions that simulated specific reactions. They varied from infiltration to necrosis of the skin. In 20 cases of open pulmonary tuberculosis, he found negative reactions, a few of which were in patients who reacted to 1 to 1000 and 1 to 10,000 dilutions of tuberculin. He considered the reaction to be due to urinary salts. Georgi (11) also believed the reaction due to urinary salts. Grass (12) also reported negative findings. Carroll and Gibson, Lewis, Korns and Hayman repeated Wildbolz's work in the United States. Carroll and Gibson (13) (14) believed the test to be of real diagnostic and prognostic importance in the majority of the cases. Lewis (15) concluded that the reaction was due to two causes, namely, the hypersensitiveness of the skin and the chemicals in the urine. Korns (16) stated the test was not practically helpful, inasmuch as it would be unsafe in doubtful cases to use the test as a criterion of activity. Hayman (17) thought that a definite positive reaction, properly controlled, was indicative of active tuberculosis and that a negative test was of less value.

From the literature one gathers that all investigators obtained skin reactions in a large percentage of cases. The important question which has been raised, however, is whether the reaction is specific and caused by tuberculoproteins, or whether it is due to the urinary salts. In so far as the tuberculoproteins are not easily dialyzed and the salts are, we attempted to settle this question by separating out the salts by dialysis; and thus we were able to eliminate the possible source of error that might be due to the presence of the salts. Furthermore, we decided to use guinea pigs instead of injecting human beings, who are not always willing to undertake the test on account of the painful reaction and because of the difficulty of obtaining normal healthy persons to act as controls. Guinea pigs react and are very sensitive to tuberculin. The reaction can be easily controlled and there is no question as to whether the subject is tuberculous or whether the disease is active.

METHODS

The urines were obtained from the tuberculosis wards of Bellevue Hospital, through the courtesy of Dr. James Alexander Miller. The morning specimen of urine was collected in a sterile container and filtered into a sterile graduate cylinder. The quantity was noted. The urine was then transferred to a side-arm distilling flask, of about a litre capacity, and closed with a rubber stopper, through the centre of which a thermometer was inserted, so that the tip touched the surface of the urine when evaporation was completed. The flask was next placed in a water-bath, the temperature of which was not to surpass 80°C. nor to go lower than 70°. The side-arm was attached to a suction pump by heavy rubber tubing. The temperature of the evaporating urine was closely observed and not permitted to rise above 55°C. The evaporation was allowed to continue until approximately one-tenth the original volume was reached. The urine was then placed in the ice-chest and, after chilling, was filtered through sterile filter paper or filter paper containing 2 per cent phenol solution. Part of the filtrate was set aside to be injected whole intracutaneously. The other part was placed into a fishskin sac for dialysis against running water, in order to dialyze out the salts. The dialysis was continued for six hours. The concentrated urine, before and after dialysis, was injected intracutaneously into tuberculous guinea pigs and into normal guinea pigs used as controls. The injections were made after the method of Mantoux, 0.2 cc. being used. The reaction of the urine was controlled by the injection of O. T. in 1 to 100 dilution into the tuberculous and normal guinea pigs.

RESULTS

Immediately following the intracutaneous injection of the concentrated urine a reaction appeared. At first, a change in the color of the skin at the point of injection was seen which took on a reddish hue. Within a half-hour a small area of necrosis developed in the centre of the inflamed skin. The necrotic area, after a time, was covered by a scab, which persisted for as long as a week before falling off. A scar then marked the

TABLE 1

CASE	DIAGNOSIS	SPUTUM	TUBERCULOUS GUINEA PIGS			NORMAL GUINEA PIGS		
			Concentrated urine	Dialyzed concentrated urine	O.T. 1 to 100	Concentrated urine	Dialyzed concentrated urine	O.T. 1 to 100
1847	Tbc. Act. I	+	+	−	+	+	−	−
1953	Tbc. Act. III	−	+	−	+	+	−	−
2050	Tbc. Act. II	+	+	−	+	+	−	−
1941	Non-Tbc.	−	+	−	+	+	−	−
1961	Tbc. Act. II	+	+	−	+	+	−	−
1955	Tbc. Act. III	−	+	−	+	+	−	−
1951	Tbc. Ina. III	+	+	−	+	+	−	−
2866	Tbc.	0	+	−	+	+	−	−
1849	Tbc. Ina. II	−	+	−	+	+	−	−
R. D.	Tbc. Act. II	−	+	−	+	+	−	−
1956	Tbc. Ina.	+	+	−	+	+	−	−
1808	Tbc. Act. II	−	+	−	+	+	−	−
1848	Tbc. Act. I	+	+	−	+	+	−	−
2041	Tbc. Ina. I	+	−	−	+	−	−	−
2004	Tbc. Ina. III	+	+	−	+	+	−	−
1951	Tbc. Ina. III	+	+	−	+	+	−	−
1955	Tbc. Act. III	−	+	−	+	+	−	−
1844	Tbc. Act. I	+	−	−	+	−	−	−
2056	Tbc. Act. III	+	+	−	+	+	−	−
C. O.	Tbc. Act. III	+	+	−	+	+	−	−
1410	Tbc. Act. III	+	+	−	+	+	−	−
Hong	Non-Tbc.	−	+	−	+	+	−	−
1565	Tbc. Act. II	+	+	−	+	+	−	−
1977	Tbc. Act. III	+	+	−	+	+	−	−

Note: In the above table "+" means positive and "−" negative.

site of the injection. This reaction occurred in both the tuberculous and the normal guinea pigs. The injection of the dialyzed urine produced no reaction in either the tuberculous or the normal guinea pigs. In other words, the urine minus its salts produced no reaction.

The question has been raised as to whether the specific reaction is overlooked in the one produced by the urinary salts. In the dialyzed urine the antigen, consisting of tuberculoproteins, should not dialyze through the fishskin sac into the running water. And, inasmuch as no reaction takes place with this dialyzed urine, it could be assumed that no antigen is present in the urine, or that it may be present in so great a dilution as not to be able to produce a reaction. In two of the cases the necrotic reactions did not occur. It is interesting to note that in these two cases the specific gravity of the urine was low and the salts diminished in quantity. Table 1 demonstrates that in 24 cases, among which are 15 cases of active pulmonary tuberculosis, a case of pyopneumothorax and one normal case, a necrotic reaction was obtained with the urine, concentrated to one-tenth its volume, and a negative reaction with the same urine after dialysis.

CONCLUSIONS

The Wildbolz auto-urine reaction has not demonstrated a specific antigen in the urine of active tuberculosis. The reaction probably is due to the normal urinary salts.

The author is indebted to Dr. Hans Zinsser for his kind coöperation and the placing of the laboratory of the Department of Bacteriology at his disposal.

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THE TECHNIQUE OF CHEST ROENTGENOGRAPHY IN PULMONARY TUBERCULOSIS[1]

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Chest roentgenography has assumed such importance in diagnosis and the gauging of treatment in chest diseases, and especially in pulmonary tuberculosis, that every detail in its technique merits careful consideration. Since its original use there have been added not only innumerable appliances for improving the purely technical parts of the machinery and the photographic-chemical elements involved, but the effects of various postures assumed by the patients during the exposures have also been discussed, although not to the extent that might be desired to derive maximum benefit from roentgenography.

Thus, in a recent contribution, Bray (1) reports that, while studying successive radiographs of the same patient, he noticed certain changes in the densities seen in the X-ray plate, which he at first attributed to faulty technique, but he subsequently discovered them to be associated with the type and depth of the inspiration employed by the patient preparatory to the X-ray exposure.

The shadow mutations, due to this cause, were at times striking. Bray finally studied these further, comparing the height of suspended costal inspiration and the height of suspended diaphragmatic inspiration. Posterior exposures were preferred to the usual anterior exposure, because on abdominal breathing the thorax does not remain in contact with the film, owing to the protrusion of the abdomen, thus causing a technical difference which might prove confusing in a study of this nature. Exacting standards were employed in the details of the X-ray technique. On costal inspiration expansion of the lung is manifested by an increase in the circumference of the chest; while on diaphragmatic inspiration the chest remains immobile, and expansion is effected solely by the descent of the diaphragm. The direction in which the lung expands affects its shape. It is relatively short and thick on costal inspiration, but long and narrow on diaphragmatic inspiration. Inasmuch

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as the hila move in unison with the diaphragm, the hilar shadows may be two interspaces lower in diaphragmatic than in costal inspiration, and there may be distinctly appreciable changes in both outline and density. Annular shadows may be present in one and absent in the other. In certain instances shadows ordinarily termed "hard," and regarded by some observers as denoting fibrosis and inactivity, may be converted into shadows which are "soft" and commonly interpreted as evidence of an active lesion. Unfortunately, Bray's study apparently covered only a few cases and left much to be desired in the way of completeness, although the points he makes are clear cut and well defined. In concluding he states that

> it has been suggested that the film on costal breathing best serves for a pathological interpretation of tuberculosis. This supposition, however, it not supported by any known facts. Moreover, it is obvious that numerous transitions may be obtained in the mutations by regulating the extent of participation of the costal and diaphragmatic elements during the inspiratory act. The causal factor of these mutations cannot reasonably be attributed to pathological changes within the lung, since the time interval between the X-ray exposures was well within one minute. Nor can the difference between the respective volumes of air intake on costal and diaphragmatic breathing be regarded as an important contributory factor, inasmuch as the air intake as registered by the spirometer varied only from 12 to 20 per cent in favor of costal breathing. The mutations are associated with the type of respiration and their presence probably can best be explained by the theory that the X-rays impinge on lesions, which, in common with the rest of the lung, have changed their shape with the type of breathing. The occurrence of these mutations is especially to be remembered in studies devoted to the correlation of the roentgenography and pathology of tuberculosis. It would seem inadvisable to employ a strictly pathological nomenclature in interpreting pulmonary shadows, a terminology descriptive of the pulmonary shadows would perhaps be better.

As Bray's study was apparently made on only a few cases it seemed advisable to elaborate on this and therefore the series to be reported in this paper included 36 cases.

In the preliminary studies the technique used by Bray was carefully adhered to, in making chest roentgenographs of 25 cases of pulmonary tuberculosis (23 of them males). Our purpose was to obtain more detailed data on tuberculosis patients and, if possible, from this information to arrive at a more standardized technique for taking chest

roentgenographs. In brief, Bray's technique consisted of taking a posterior-anterior plate with standard and uniform methods, once during suspended costal inspiration and, as soon as possible thereafter, during suspended diaphragmatic inspiration.

In our second series, consisting of 5 male and 5 female patients with pulmonary tuberculosis, roentgenographs were made in both the posterior-anterior (Bray's technique) and the anterior-posterior positions (the usual routine position for taking roentgenographs),[2] and in each position during suspended costal and during suspended diaphragmatic inspiration. In order to obtain roentgenographs without interference during the different types of breathing a suitable stand was devised for holding the X-ray plates which permitted free costal and abdominal movements of the patient.

THE ROENTGENOGRAPH OBTAINED IN THE POSTERIOR-ANTERIOR POSITION DURING SUSPENDED COSTAL OR DIAPHRAGMATIC INSPIRATION

The 25 patients studied in this position consisted of 23 males and 2 females, and are classified, as nearly as possible, into questionable, incipient, moderately and far advanced types of pulmonary tuberculosis. Such details of taking the roentgenograph as the distance of the target, the exposure time, the use of the intensifying screen, etc., are so well known that it does not seem necessary to enter into their minutiae here. There are many factors involved in making a roentgenograph, and, whereas one roentgenologist prefers a soft picture to bring out the pathological changes, another may prefer one of sharp contrasts, yet the pictures may be of equal value in revealing changes. It is also well known that with proper target distance the proximity of the object from the plate to a great extent determines the sharpness of its definition. But since roentgenographs hardly picture true pathological changes in the strict sense of the term, but reveal only shadows and densities of varying grades with no regard for very fine detail, it is easily seen that the larger and more important shadows may be discernible in different positions and with different techniques, even though for the sake of accurate determination it may be advisable to bring out more clearly a certain indeterminate shadow in a special case for the purpose of better interpretation. When, however, only one plate can be taken the question naturally arises of how the maximum diagnostic value may be had from one type of exposure to be used as a routine.

[2] By "anterior-posterior" is meant that the patient faces the plate with back to the X-ray tube.

ROENTGENOLOGICAL REPORTS ON CASES OF PULMONARY TUBERCULOSIS WITH PLATE MADE ACCORDING TO BRAY'S TECHNIQUE

Questionable and Incipient Cases:

Case 1: H. F. Questionable.[3] Apices on both sides slightly clouded, with linear markings accentuated over both lungs, more marked in lower lobes. In the plate taken during arrested diaphragmatic inspiration the clavicles are lower, the heart is pulled slightly to the left and the shadows appear softer than in the plate taken during arrested costal inspiration. It could not be determined whether the diaphragmatic or costal plate was of greater value.

Case 2: H. G. Questionable. Suspicious clouding of right upper lobe at periphery opposite third, fourth and fifth ribs in midaxillary line. Apices clear; moderate beading of bronchi in both lower lobes. In plate taken during arrested diaphragmatic inspiration the clavicles are lower, the heart shadow is pulled to the left and the chest outline narrower than in the costal plate; otherwise, the differences between the two plates were only slight.

Case 3: H. Z. Incipient. Apices on both sides present slight cloudiness, suggesting early inflammatory reaction. Otherwise, the plates reveal no pulmonary abnormalities. In plate taken during suspended diaphragmatic inspiration, the clavicles and the diaphragm are lower than in plate taken during suspended costal inspiration; otherwise, the plates present no perceptible differences.

Moderately and Far Advanced Cases of Pulmonary Tuberculosis:

Case 4: S. L. Female. Moderately advanced. Both lungs infiltrated with small nodular densities which appear to be undergoing calcification, and there is some fibrous infiltration of hila, with lymph node enlargement. In plate taken during arrested diaphragmatic inspiration the diaphragm is about half an interspace lower than in plate taken during arrested costal inspiration. Otherwise, there are no perceptible differences between the two plates.

Case 5: B. W. Moderately advanced. Right upper lobe quite dense, with apparently old healed lesion near periphery. All linear markings are increased in right lung. Left upper lobe similar to right, but less dense, suggesting more recent involvement. Bronchial markings increased; hila on both sides show increased densities and lymph node involvement with calcification in places. There is a pericardial adhesion to diaphragm. In plate taken during suspended diaphragmatic inspiration the clavicles are lower, the shadows in the left upper lobe softer and the chest outline narrower than in plate taken during arrested costal inspiration.

[3] All diagnoses are clinical diagnoses.

Case 6: F. P. Far advanced. Dense infiltration of left apex, with peribronchial thickening and beading, extending to periphery throughout remainder of left lung. Peribronchial thickening, with fibrous and inflammatory infiltration, throughout right lung, and an annular shadow, possibly a cavity, just below clavicle in right upper lobe. Tenting of left diaphragm. In diaphragmatic inspiration plate the clavicles and the diaphragm are lower, the outlines of the chest narrower and the shadows softer than in costal inspiration plate. The tenting of the left diaphragm is more defined in the roentgenograph taken during suspended costal inspiration; otherwise, there are no perceptible differences.

Case 7: L. K. Far advanced. Right apex very cloudy. Marked inflammatory mottling and fibrosis extending throughout entire right lung. Left apex slightly cloudy with peribronchial thickening and beading extending throughout entire left lung. Fibrous infiltration of hila with lymph node enlargement. During suspended diaphragmatic inspiration the clavicles are lower and the heart is pulled slightly more to the left than during costal inspiration. There are no marked differences in the pulmonary shadows in this case.

Case 8: E. D. Far advanced. Fibrous and inflammatory mottling of entire left lung. Marked fibrosis, interspersed with inflammatory mottling over entire right lung. Large area of rarefaction, from second to fourth ribs anteriorly, and from hilum to periphery of right lung. Marked infiltration of both hila and lymph nodes enlarged. Adhesions extending to both diaphragms. These findings occur in both plates, and the plates differ only in that during arrested diaphragmatic inspiration the shadows due to inflammatory reactions seem softer, the clavicles and diaphragm are lower and the heart shadow is narrower.

Case 9: M. S. Far advanced. Entire right lung mottled with dense shadows and left lung also densely involved in upper portion. The two plates differ only in that the heart is pulled slightly more to the left, the clavicles are a little lower and the shadows a little softer in the plate taken during suspended diaphragmatic inspiration.

Case 10: A. G. Far advanced. Consolidation of both apices with marked fibrosis and inflammatory mottling of upper lobes of both lungs. Annular shadows in both upper lobes. The remainder of both lungs reveals peribronchial thickening and infiltrations. The plate taken during suspended diaphragmatic inspiration reveals the usual lowering of the clavicles and diaphragm in comparison with the costal plate; otherwise, the two plates compare well.

Case 11: O. G. Far advanced. Both apices consolidated, the left being more marked. Peribronchial thickening and infiltration throughout remainder of both lungs. Slight tendency to calcification. Usual findings regarding clavicles and heart; otherwise, the two plates, taken during suspended diaphragmatic and costal breathing, compare well.

Case 12: L. S. Far advanced. Marked fibrosis and inflammatory infiltration in upper lobes of both lungs. Linear markings accentuated in lower lobes. Marked fibrous and lymph node enlargements at hila. Adhesions to diaphragm on both sides. Mediastinum pulled to right in upper half. No perceptible difference between plates taken during diaphragmatic and costal inspiration.

Case 13: A. Y. Far advanced. Marked fibrous infiltration of entire left lung, with some inflammatory mottling in upper lobe. Consolidation in apex and upper portion of right upper lobe, with large cavity just below clavicle. Marked fibrous infiltration and lymph node enlargement of both hila. Adhesions to diaphragm on both sides. Shadows distinctly softer in diaphragmatic plate. Usual findings with the clavicles and heart, although latter pulled slightly more to left.

Case 14: H. B. Far advanced. Marked fibrosis and inflammatory mottling of both lungs; more marked, however, in upper lobes. Annular shadow opposite second rib anteriorly in left upper lobe. Hila show fibrous infiltration and lymph node enlargements. Clavicles and diaphragm about one interspace lower and shadows softer in plate taken during diaphragmatic inspiration as compared with costal plate. Otherwise, no distinct differences.

Case 15: L. W. Far advanced. Consolidation of left apex, with large annular shadow just below clavicle. Fibrous and inflammatory mottling over remainder of left lung. Consolidation of upper portion of right upper lobe with peribronchial thickening; fibrous and inflammatory infiltration extending to the diaphragm on both sides. Diaphragmatic and costal plates show very little difference, except that in former the clavicles are slightly lower.

Case 16: S. K. Far advanced. Marked fibrosis with inflammatory mottling and annular shadows, which are probably cavities, in upper lobes of both lungs. Linear markings greatly accentuated, and marked parenchymal infiltration throughout lower lobes. Adhesions to the diaphragm on both sides. Clavicles and diaphragm a little lower in plate taken during suspended diaphragmatic inspiration, and shadows are little softer and chest outline narrower than in plate taken during suspended costal inspiration.

Case 17: C. G. Far advanced. Both apices cloudy, with fibrous and inflammatory mottling. Cavities in upper lobes of both lungs. Peribronchial thickening and parenchymal infiltration throughout remainder of both lungs. Heavy fibrous and lymph node shadows at hila. Pericardium adherent to diaphragm. Clavicles and diaphragm lower, heart shadow narrower, chest outline narrower and pulmonary shadows as a whole softer in plate taken during suspended diaphragmatic inspiration.

Case 18: J. N. Far advanced. Inflammatory mottling, with honeycomb appearance, in upper lobes of both lungs. Marked infiltration throughout

lower lobes of both lungs. Lymph node and fibrous infiltration of hila. Adhesions to diaphragm on both sides. Only discernible difference between the two plates is lower position of clavicles and narrowing of chest outline during diaphragmatic inspiration.

Case 19: L. L. Far advanced. Marked fibrous and inflammatory infiltration, extending over entire left lung. Dense fibrous ring with rarefied centre, probably cavity, opposite second interspace anteriorly. Right apex turbid and all linear markings throughout right lung accentuated. Adhesion to left diaphragm and cardiac dimensions increased. The two plates reveal very little detailed differences.

Case 20: J. M. Far advanced. Peribronchial thickening, with fibrous and inflammatory mottling over entire left lung. Marked fibrous consolidation of right upper lobe, with several small cavities and one large cavity with fluid level opposite third and fourth interspaces anteriorly. Tenting of diaphragm on right side. Narrowing of chest outline and softening of shadows on diaphragmatic plate are only discernible differences.

Case 21: T. T. Far advanced. Marked fibrosis and inflammatory mottling, extending over both lungs. Changes more marked in right upper lobe, where there is large area of consolidation, in centre of which is rarefied area, probably cavity. Mediastinum and heart pulled to right. In plate taken during suspended diaphragmatic inspiration clavicles and diaphragm are lower and chest outline narrower than in the one taken during suspended costal inspiration; otherwise, no perceptible differences.

Case 22: R. G. Far advanced. Fibrosis and inflammatory mottling over entire left lung, with large annular shadow just below clavicle in upper lobe. Linear markings accentuated, and slight infiltration of right lung. Aside from the usual changes in position of clavicle, the two plates show no differences.

Case 23: B. S. Far advanced. Accentuation of all linear markings, with a small amount of infiltration of entire left lung. Consolidation of apex, and large rarefied area from clavicle to lower border of second rib anteriorly in right lung. Extensive fibrosis and thickened pleura at right base. Mediastinum and heart pulled to right. Adhesions to diaphragm on both sides. Clavicles about one-half inch lower in plate taken during suspended diaphragmatic inspiration; otherwise, no other distinguishing features.

Case 24: A. W. Far advanced. Marked fibrosis and inflammatory mottling in both upper lobes, with marked fibrosis also present in both lower lobes. Clavicles and diaphragm each about one interspace lower; heart shadow lengthened; parenchymal shadows softer; and an adhesion in right costophrenic angle, that shows in plate taken during suspended diaphragmatic inspiration in distinction to the plate taken during suspended costal inspiration.

Case 25: J. H. Far advanced. Fibrosis and inflammatory mottling over both lungs, and large annular shadow in right upper lobe, probably cavity. Hila show fibrosis and lymph node enlargement. Adhesion to right diaphragm more pronounced in costal plate. Clavicles and diaphragm are lower and heart shadow and chest outline narrower in plate taken during suspended diaphragmatic inspiration; and annular shadow in upper part of upper lobe of right lung which is not seen in plate taken during suspended costal inspiration. The annular shadow beneath the above described one shows on plates taken in both types of breathing, but is of different shape. There is a distinct annular shadow on the diaphragmatic plate and a honeycomb appearance on the costal plate.

In summary, then, there were 2 of the 25 cases of which roentgenographs were taken according to Bray's technique, in which the plate taken during suspended diaphragmatic inspiration revealed findings not discernible in the plate taken during suspended costal inspiration. In one of these cases there was an adhesion in the right costophrenic angle, and in the other there was an annular shadow in the upper part of the upper lobe of the right lung that was only visible in the plate during suspended diaphragmatic inspiration. Both of these findings were in far advanced cases. In one case (*6*) the tenting of the diaphragm was more defined in the plate taken during suspended diaphragmatic inspiration. In practically all the cases the clavicles and diaphragm were lower, the heart and mediastinal shadows narrower and longer, the chest outline narrower, and the lung parenchymal shadows softer in the plate taken during suspended diaphragmatic inspiration than in that taken during suspended costal inspiration.

Having thus found that a certain small percentage of cases may reveal more in the way of positive findings when the roentgenograph was taken during suspended diaphragmatic inspiration than in suspended costal inspiration in the posterior-anterior position used by Bray, it was deemed advisable to study in a comparative manner roentgenographs thus taken, as well as those taken in the usual anterior-posterior position during suspended diaphragmatic inspiration and suspended costal inspiration. Every effort was made to obviate any interfering movement occasioned by the breathing in changing from one type of inspiration to the other. In these studies the plates were all taken consecutively, and with as little loss of time as possible in changing from one position to the other or from one type of breathing to the other. Thus 4 plates

were made of the chest of each of 11 patients in the posterior-anterior position to the plate (Bray) during diaphragmatic and costal inspiration, and in the anterior-posterior position to the plate (the usual routine technique) during diaphragmatic and costal inspiration.

Case 26: F. P. Female. Questionable. All linear markings accentuated, especially those of descending type. Some beading, but very little parenchymal infiltration. Fibrosis and lymph node enlargement of hila; lymph nodes tending to calcify. No perceptible difference in pulmonary findings of four plates taken in the different positions and during the different types of inspiration.

Case 27: J. M. Female. Incipient. In posterior-anterior plates both apices slightly cloudy, and small areas of inflammatory mottling, following the bronchi toward hilum on both sides. Hilum lymph nodes on both sides slightly enlarged. Bases on both sides show thickened bronchi with nodular beading. It seems that the linear markings are more distinct and infiltration more marked in plate taken during suspended costal inspiration—contrary to the previous findings recorded above. Clavicles an interspace lower in plate taken during suspended diaphragmatic inspiration. In plates taken in anterior-posterior position the shadows stand out more clearly during suspended costal inspiration. Apices distinctly more visible in plate taken during suspended diaphragmatic inspiration; in this case being contrary to the usual rule.

Case 28: F. R. Incipient. In posterior-anterior position of patient, an accentuation of bronchial markings below clavicle in upper lobe of left lung with surrounding slight inflammatory mottling. Remainder of lung fairly normal. Only difference between diaphragmatic and costal inspiration plates is slightly lower position of clavicles in former. In anterior-posterior position there is seen a narrowing of the heart shadow during suspended diaphragmatic inspiration, but, as a whole, the four plates show very little difference in pulmonary findings.

Case 29: I. S. Female. Moderately advanced. In posterior-anterior position a peribronchial thickening, with fibrosis and inflammatory mottling in upper lobes; more marked, however, on the right side. Descending linear markings accentuated. Marked fibrosis and lymph node enlargement of hila with tendency to calcification. Plates reveal no appreciable difference in pulmonary findings during diaphragmatic and costal inspiration. Likewise, plates taken in anterior-posterior posture reveal no appreciable difference in pulmonary findings from those taken in posterior-anterior position; and only difference between plates taken during diaphragmatic and costal inspiration is that in former the clavicles and diaphragm are lower than in latter.

Case 30: M. G. Moderately advanced. In posterior-anterior and anterior-posterior positions is seen a peribronchial infiltration of fibrous type, extending throughout both lungs, but more pronounced in left lung. Aside from lower position of clavicles and softer appearance of shadows during the suspended diaphragmatic inspiration, there are practically no differences.

Case 31: M. W. Moderately advanced. In the four plates there is cloudy mottling of left apex and peribronchial thickening throughout entire left lung. In upper lobe of right lung there is fibrosis and inflammatory mottling, present, however, less throughout middle and lower lobes. Fibrosis and lymph node enlargement of hila. Except for usual changes in position of clavicles and diaphragm, pulmonary findings are about the same in the four plates.

Case 32: M. R. Moderately advanced. The four plates taken during posterior-anterior and anterior-posterior positions show usual differences, being probably greater in posterior-anterior position during diaphragmatic and costal inspiration than in anterior-posterior. Differences, however, of no practical significance.

Case 33: P. S. Moderately advanced. The four plates taken in posterior-anterior and anterior-posterior positions show usual differences, but give no information of practical significance.

Case 34: B. W. Female. Far advanced. In posterior-anterior position plates show much congestive mottling of pulmonary parenchyma, with many small areas of calcification scattered throughout both lungs. Right lung shows more pathological change than left. Lymph nodes at hila calcified. No striking differences between two plates taken during suspended diaphragmatic and costal inspiration, but shadows appear denser and stand out more distinctly in latter plate. In anterior-posterior position clavicles about one interspace lower in plate taken during suspended costal inspiration, but shadows appear harder and more distinct in latter. However, no striking differences.

Case 35: J. M. Far advanced. In posterior-anterior position dense shadows in upper lobe of left lung, and large annular shadow, probably cavity, just below clavicle. Marked mottling of remainder of left lung. Right lung shows marked fibrosis and inflammatory mottling in upper lobe and to lesser degree in middle and lower lobes. Hila show dense shadows of infiltration and lymph node enlargement. Clavicles and diaphragm lower in plate taken during suspended diaphragmatic inspiration; otherwise, findings identical in the two. Plates taken in anterior-posterior position show about same pathological changes as those taken in posterior-anterior position, and clavicles and diaphragm are lower and shadows softer in plate taken during suspended diaphragmatic inspiration.

Case 36: D. K. Female. Far advanced. In posterior-anterior position plates show marked fibrosis and inflammatory mottling of both lungs. Mottling more pronounced during suspended costal inspiration. Distinct annular

shadow opposite clavicle in upper lobe of right lung during suspended costal inspiration, which is indistinct during suspended diaphragmatic inspiration, and the honeycomb appearance of shadows seen below clavicle during costal inspiration changes to large rarefied area during diaphragmatic inspiration. The heart shifts slightly to the left during diaphragmatic inspiration and the space above the clavicles is larger. Adhesion between pericardium and diaphragm. In plates taken in anterior-posterior position during suspended diaphragmatic inspiration, shadows seem softer than when taken during suspended costal inspiration, but there are no other characteristic differences. As a whole, pulmonary findings resemble those seen in plates taken during posterior-anterior position.

In summarizing the findings in the roentgenographs of these 11 patients we find that there was only one in which the findings differed perceptibly from the others in the one type of plate. Although it must be admitted, from the studies on both series of patients, that about 10 per cent of the cases reveal what might be considered additional pathological findings when plates are taken both during suspended diaphragmatic and suspended costal inspiration, the above study, considering cases 24, 25 and 36, would leave us in doubt as to which type of breathing to prefer were we limited to the use of one plate. For maximum diagnostic value, which from the practical standpoint might be considered more of academic significance, both plates should be taken, but from a purely economic and practical viewpoint it is difficult to recommend the taking of more than one plate, and the choice lies with the individual technician. In the important individual case, however, when detailed information is desired and economy can be neglected it is to be recommended that at least two exposures be made during suspended diaphragmatic and suspended costal inspiration, either in the posterior-anterior or in the anterior-posterior position. Although the number of incipient cases was few in this study, it is probably significant that the 3 cases in which the plates revealed differences during the two types of inspiration were far advanced. Sight must not be lost of the fact that the proximity of the densities to the plate were reversed in the two positions, yet this change in position played very little part in affecting the general aspect of the roentgenographs from the standpoint of even visible finer pathological changes.

SUMMARY

In a comparative study of roentgenographs, taken in the posterior-anterior position during suspended diaphragmatic inspiration and sus-

pended costal inspiration on 25 patients with pulmonary tuberculosis, there were found 2 cases of far advanced pulmonary tuberculosis in which the roentgenograph taken during suspended diaphragmatic inspiration revealed changes of a definite nature which were not revealed in the roentgenograph taken during suspended costal inspiration, thus corroborating Bray's observations.

In a series of 11 cases of pulmonary tuberculosis, of which roentgenographs were taken in the posterior-anterior position and the anterior-posterior position during suspended diaphragmatic and suspended costal inspiration, there was found one case (far advanced pulmonary tuberculosis) in which the roentgenographic findings differed during suspended diaphragmatic and suspended costal inspiration. In spite of these findings, and as a result of a general survey of the situation, considering the diagnostic value of these differences and the economic side of the question, it can hardly be recommended that for general diagnostic purposes in pulmonary tuberculosis more than one type of position and inspiration be used. The matter of choice for general use rests entirely with the individual case. For purely academic or research purposes, however, and to obtain the maximum detailed information on an individual case, it is recommended that at least both types of inspiration be used and, if possible, the two positions, posterior-anterior and anterior-posterior, be taken.

The author wishes to acknowledge and express her appreciation to Drs. Saling Simon and Samuel Swezey for their kind coöperation in the painstaking reading of all the roentgenographs reported in this contribution.

REFERENCE

(1) Bray, H. A.: Mutation of pulmonary shadows due to type of breathing, Amer. Jour. Roentgenol., 1922, ix, 628.

Figs. 1. and 2. Case 24: Roentgenographs of Case of Far Advanced Pulmonary Tuberculosis, Taken in Posterior-Anterior Position

Fig. 1 was taken during suspended diaphragmatic inspiration and fig. 2 during suspended costal inspiration.

Note arrow in right costophrenic angle in fig. 1, indicating adhesion not visible in fig. 2. In so far as pulmonary changes are concerned the two figures compare fairly well in their gross findings.

Figs. 3, 4, 5 and 6. Case 33: Roentgenographs of Case of Far Advanced Pulmonary Tuberculosis

Figs. 3 and 4 taken in posteror-anterior and figs. 5 and 6 in anterior-posterior position. Figs. 3 and 5 taken during suspended diaphragmatic inspiration and figs. 4 and 6 during suspended costal inspiration.

For practical purposes the four figures show very little difference in the pulmonary pathological changes.

Fig. 1

Fig. 2

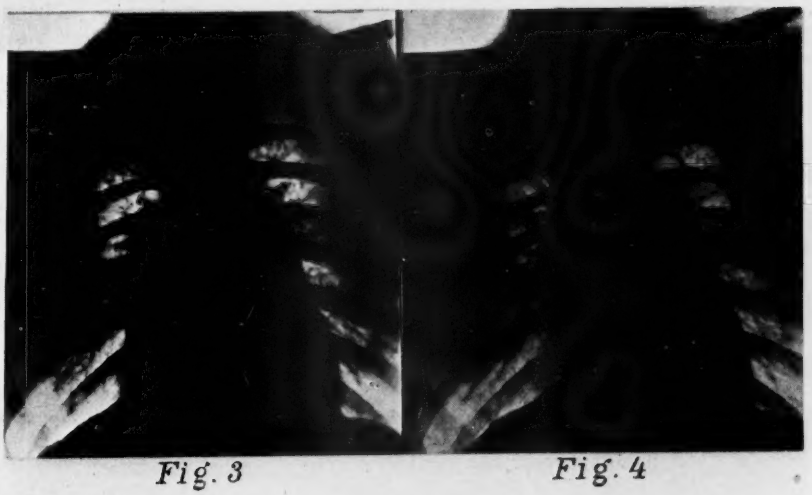

Fig. 3

Fig. 4

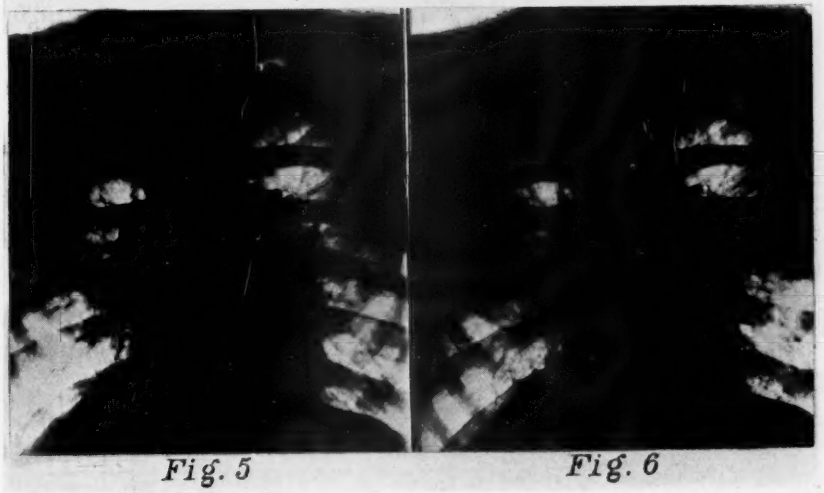

Fig. 5

Fig. 6

FIGS. 7 AND 8. CASE 25: ROENTGENOGRAPHS OF CASE OF FAR ADVANCED PULMONARY TUBERCULOSIS TAKEN IN POSTERIOR-ANTERIOR POSITION

Fig. 7 taken during suspended diaphragmatic inspiration and fig. 8 during suspended costal inspiration.

Note annular shadow (cavity) in the upper part of the upper lobe of the right lung (see arrow) in fig. 7 not seen in fig. 8. Below this is another annular shadow which in fig. 8 has a honeycombed appearance.

FIGS. 9, 10, 11 AND 12. CASE 36: ROENTGENOGRAPHS OF CASE OF FAR ADVANCED PULMONARY TUBERCULOSIS

Figs. 9 and 10 taken in posterior-anterior and figs. 11 and 12 in anterior-posterior position. Figs. 9 and 11 taken during suspended diaphragmatic inspiration and figs. 10 and 12 during suspended costal inspiration.

There is an annular shadow (see arrow) in the upper lobe of the right lung opposite clavicle in fig. 10, taken with the patient in the posterior-anterior position during suspended costal inspiration, which is indistinct during diaphragmatic inspiration (fig. 9), and the honeycombed appearance of the shadows seen below the clavicle in fig. 10 changes to a large rarefied area in fig. 9. In the anterior-posterior position the annular shadows are absent.

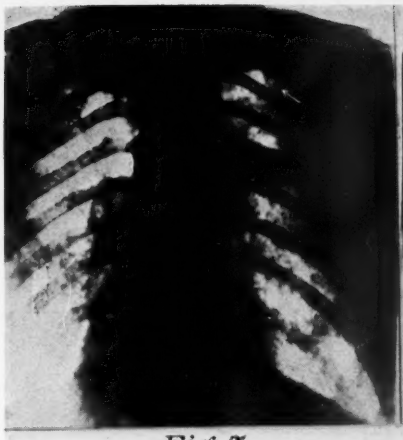

Fig. 7

Fig. 8

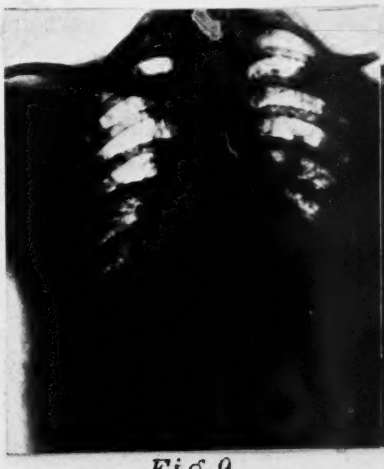

Fig. 9

Fig. 10

Fig. 11

Fig. 12

THE PULMONARY ASPIRATION OF PARTICULATE MATTER AND PULMONARY TUBERCULOSIS PRODUCED EXPERIMENTALLY BY ASPIRATION[1]

(Addendum)

H. J. CORPER

In a previous communication by Corper and Robin (1) it was reported that, while particulate matter inhaled as smoke or soot (carbon suspended in air) localized early, mainly in the larger air passages of the respiratory tract and in certain definite localities, namely, on histological projections at the bifurcations of the air passages, and only after prolonged inhalation deposited in the smallest respiratory divisions (the alveoli) and then only in comparatively small amount, the same material (carbon), when inspired or aspirated in *fluid suspension*, had a tendency to be taken immediately into the finest pulmonary divisions where the greater part of the particulate matter was retained for a relatively long time. At that time intervals up to fifteen weeks were studied and recorded.

Inspired or aspirated fluid suspensions of particulate matter (india ink) localize in the lungs of animals, depending upon the posture in which the animal is held during the entrance of the fluid into the lungs. In the horizontal posture, during ether anesthesia, in rabbits and dogs, india ink, following nasal instillation with the head slightly elevated, is found mainly in the upper lobe of the right or left lung, depending upon whether the animal lay on its right or left side during instillation. Normally, in the horizontal posture and without anesthesia, fluids do not readily enter the lungs, although in the upright (vertical) posture, with the head slightly extended, the fluid readily enters the lungs of those animals that are normally accustomed to the horizontal posture. It enters rather more easily in the rabbit than in the dog, and tends to localize mainly in the lower lobes of the lungs, the localization of the aspirated fluids being largely determined by gravity and inspiratory suction.

[1] From the Research Department, National Jewish Hospital for Consumptives, Denver, Colorado.

Utilizing this information (2) regarding the postural localization of aspirated fluids, an upper lobe pulmonary tuberculosis, the most common type of the disease in man, was reproduced in dogs (in the sense of human postural anatomy) by the instillation of suspensions of tubercle bacilli into the nose, while the animal was lying in the horizontal posture (on the right or left side depending upon the side in which involvement was desired), during ether anesthesia and with the head slightly elevated. By means of dead human tubercle bacilli, aspirated under ether anesthesia, all of the important characteristics of the disease in man were reproduced, except progression in the true sense of the term, such as would naturally be dependent upon actual multiplication of the bacilli in the lungs. These changes, including massive tuberculous granulation tissue formation, with subsequent necrosis followed by discharge into the bronchi and resulting cavity formation, fibrous pleural adhesions and intrapulmonary capillary hemorrhages, were all obtained and in definite sequence, indicating that the full tissue damage initiated when the bacilli enter the lungs is not exhausted for a considerable period. Visible cavities were found only after one hundred and thirty-nine days, while intrapulmonary hemorrhage was regularly seen earlier (after forty-one days).

When the first cited communication on the pulmonary aspiration of particulate matter was published, there still remained alive 3 rabbits of the 12 used in experiment 2[2] of that study. These had been allowed to aspirate india ink following nasal instillation while in the vertical position with head up and extended. The purpose of this part of the study was to determine the time of persistence of the aspirated carbon in the lungs. At that time the carbon was found to persist for at least fifteen weeks (rabbit 9) in the alveoli and finer pulmonary respiratory divisions. The larger air passages at this time were comparatively free from pigment-bearing cells. The following is the later report on rabbits 10 to 12 inclusive:

Rabbit 10: Died twenty-eight weeks after nasal instillation, and revealed, besides a "snuffles" pneumonia, the carbon deposits in discrete spots, posteriorly in the lower lobes of both lungs and to a slight extent in the middle lobe of the right lung. No histological study was made of this lung on account of the complicating snuffles.

Rabbit 11: Examined thirteen months after nasal instillation. Revealed the discrete carbon spots along the posterior border of the lower lobes of both lungs

[2] See AMERICAN REVIEW OF TUBERCULOSIS, 1922, vi, page 831.

and irregularly in the lower portion of the upper lobe of the right lung, none being seen in the middle lobe of the right lung or upper lobe of the left lung. Histological sections revealed the carbon in masses of different sizes in the alveoli of the lungs. There were varying grades of mild tissue reaction, ranging from a slight hypertrophy of the alveolar walls to a practically negligible change. In a few locations the perivascular and peribronchial lymphatics contained numerous phagocytic carbon-containing cells, but they were not especially conspicuous in the alveoli or alveolar walls, even in the areas contiguous to the carbon deposits.

Rabbit 12: Examined eighteen months after nasal instillation. Revealed the discrete carbon spots, of irregular size, along the posterior portion of the lower lobes of both the right and left lungs, with a few small discrete spots scattered posteriorly in the upper and middle lobes of the right lung. A few very small carbon spots were also seen in the upper lobe of the left lung. There did not seem to be any striking diminution of the carbon pigment evident to the naked eye. Sections taken from this lung in the vicinity of the carbon spots revealed very little change in the findings, so far as the histological picture was concerned, from that seen in the lungs of earlier periods. The carbon was seen as larger and smaller black masses in what appeared to be the former alveoli, with very little surrounding cellular reaction to the foreign masses. Here and there, in the air passages, were seen occasional phagocytic cells, laden with black pigment and in the walls of the alveoli, but on the whole there did not seem to be an intense reaction to the carbon foreign body. In some places, where there were many small masses of carbon, the cellular reaction seemed to be slightly more intense than where a single large deposit of carbon was seen, and a distinct and appreciably thickened alveolar wall was discernible between the different small masses of carbon. The peribronchial lymphoid areas were full of carbon pigment especially in the vicinity of the carbon deposits.

From the above additional studies on the pulmonary aspiration of particulate matter it is seen that the insoluble particulate matter (carbon), which was aspirated into the lungs in liquid suspension, may persist in the alveoli or finer air passages longer than one and one-half years thereafter, and produce at most only a mild proliferative reaction on the part of the pulmonary tissues. Thus, it is seen that particulate matter reaching the alveoli, if it is composed of such material that it cannot be dissolved in the lungs, or produce an inflammatory reaction leading to ulceration, and is too large and compact to be carried to the adjacent lymphoid tissues of the lungs and lymph nodes, may persist in the alveoli of the lungs for a relatively long time,—over one and one-half years. This is contrary to the common generally accepted idea regard-

ing the disposal of such substances from the finer respiratory divisions. Elimination of particulate matter from the larger air divisions, bronchi and bronchioles, is apparently much more rapid, as may be seen from the studies on inhaled soot which to a large extent lodges early in the larger air passages.

When the communication on *Pulmonary Tuberculosis Produced Experimentally by Aspiration* was published there still remained 3 dogs of the second series.[3] The purpose of this series was to determine the consecutive pulmonary tissue changes produced by aspirated dead tubercle bacilli, following nasal instillation during ether anesthesia in dogs. The last dog, *J*, reported on previously, was examined one hundred and thirty-nine days after nasal instillation and was the first animal of the series to reveal typical cavity formation. In this dog the pulmonary distribution was peculiar, and did not entirely conform to the postural distribution, in that there were found involvement and cavities in both lungs, a finding which could not be accounted for, in view of the fact that all the previous dogs in this experiment had shown entire conformity to the postural distribution of the tuberculosis. The following two dogs to be reported on, which had also received by nasal instillation a suspension of dead human tubercle bacilli while lying on the right side during ether anesthesia and with head slightly elevated, entirely conformed to the postural distribution of the pulmonary tuberculosis found:

Dog K: Was examined one year after nasal instillation. The lungs superficially revealed massive tuberculous involvement of the entire lower two-thirds of the upper lobe and the posterior upper border of the middle lobe of the right lung, with a strand-like adhesion to the chest wall extending from the upper lobe. There were dense fibrous adhesions between these two lobes of the right lung. The lower lobe of the right lung and the entire left lung were free from tuberculosis. On cutting through the involved areas, there was found one large cavity in the lower mid-portion of the upper lobe, about 0.5 to 1 cm. in diameter, which communicated with another smaller cavity. There were no cavities in the middle lobe. The walls of the cavities were smooth and glistening, although slightly discolored with pigment, either of blood or of anthracotic origin, and in a few spots appearing to be of the nature of young granulation tissue. Microscopically, the cavity was found to communicate with a bronchus and the walls were composed of a granulation tissue of mature type. As a whole, the sections resembled those seen in dog *J*, previously reported.

[3] See AMERICAN REVIEW OF TUBERCULOSIS, 1922, vi, page 861.

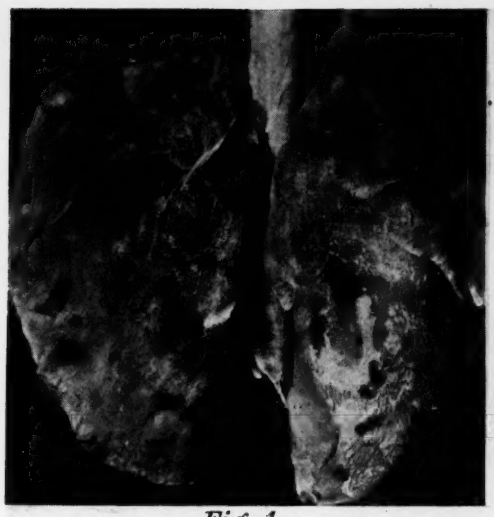

Fig. 1

Fig. 4

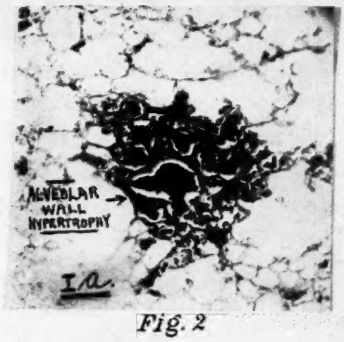

Fig. 2

Fig. 5

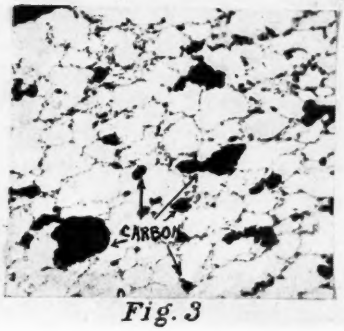

Fig. 3

Fig. 6

FIG. 1. PHOTOGRAPH OF RABBIT'S LUNG (RABBIT 12) 1½ YEARS AFTER THE PULMONARY ASPIRATION OF INDIA INK

FIG 2. PHOTOMICROGRAPH OF SECTION OF LUNG SHOWN IN FIG. 1

Hypertrophy of alveolar walls in vicinity of small accumulations of carbon (low magnification).

FIG. 3. PHOTOMICROGRAPH OF SECTION OF LUNG SHOWN IN FIG. 1

Lack of appreciable reaction to the carbon when in small single accumulations (low magnification).

FIG. 4. PHOTOGRAPH OF DOG'S LUNG (DOG L) 1½ YEARS AFTER THE PULMONARY ASPIRATION OF DEAD HUMAN TUBERCLE BACILLI IN FLUID SUSPENSION

Note tuberculous involvement in the upper portion of the right lung and a cavity "a" (opened) in the upper lobe and another "b" (opened) on the upper border of the lower lobe

FIG. 5. ENLARGEMENT OF THE CAVITY IN THE UPPER LOBE OF LUNG SHOWN IN FIG. 4

FIG. 6. ENLARGEMENT OF THE CAVITY IN THE LOWER LOBE OF LUNG SHOWN IN FIG. 4

Cavity cut open showing the walls of each half

Dog L: Was examined one and one-half years after nasal instillation. The lungs superficially revealed a massive tuberculous involvement of the upper and middle lobes of the right lung, with dense interlobar fibrous adhesions, and a fibrous adhesion extending to the chest wall anteriorly. There was slight involvement seen superficially on the upper margin of the lower lobe of the right lung, but there were no interlobar adhesions visible here. The entire left lung was free from tuberculous involvement. On cutting into the upper lobe in the vicinity of the tuberculous involvement, there was seen a fairly large single cavity, about 1 to 1.5 cm. in diameter, with smooth glistening fibrous tissue walls, mottled with a gray-black pigment and seemingly of blood or of anthracotic origin. There were no cavities in the middle lobe, although dense fibrous interlobar adhesions bound the upper and middle lobes together. On cutting into the upper edge of the lower lobe of the right lung, there was found a large oval cavity, about 0.5 to 1 cm. in diameter, with a fibrous tissue strand extending across the centre, and mature granulation tissue walls. Microscopically, the cavities were found to be composed of mature granulation and fibrous tissue. In general there was a marked resemblance to the histological findings obtained in dogs *J* and *K*, except that the more mature fibrous tissue of healing predominated in the sections taken from the involved areas in dog *L*.

One dog, *M*, of this series is still alive and will be reported on at a later date, if the findings differ sufficiently from the above to warrant an individual note on this animal.

In the upper lobe pulmonary tuberculosis reproduced in dogs (in the sense of human postural anatomy) by the instillation of suspensions of dead tubercle bacilli into the nose, while the animal is lying in the horizontal posture (on the right side in these experiments), during ether anesthesia and with the head slightly elevated, visible cavities were found after one hundred and thirty-nine days and persisted for one and one-half years. After one and one-half years the destructive process occasioned by the dead bacilli had evidently come to an end, and complete fibrous tissue repair exists, but cavities still persist at this time with, however, apparently completely fibrosed walls.

SUMMARY

Particulate matter (carbon) in fluid suspension, aspirated into the lungs of rabbits, is still found in appreciable amount in the alveoli of these animals one and one-half years after aspiration following nasal instillation. There is present at this time a mild proliferation and hypertrophy of the alveolar walls in the vicinity of the carbon masses, although in places this reaction may be only slight.

Cavities are still present in the upper portions of the right lung in dogs one and one-half years after the pulmonary aspiration of dead human tubercle bacilli, following the nasal instillation of fluid suspensions of these bacteria during anesthesia and with the animal lying in the horizontal position and on the right side. The destructive part of the tuberculous process had apparently terminated at this time and the cavities are lined with mature fibrous tissue walls. The earliest appearance of cavity was in a dog examined one hundred and thirty-nine days after aspiration of the dead bacilli into the lungs.

REFERENCES

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(2) CORPER, H. J.: Pulmonary tuberculosis produced experimentally by aspiration, Ibid., 1922, vi, 851.

THE SOLVENT ACTION OF OLEIC ACID ON CULTURES OF TUBERCLE BACILLI[1]

FRANK A. McJUNKIN

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Since the work of Prudden and Hodenpyl (1) it has been well known that morphologically intact tubercle bacilli persist for weeks in the tissues of animals that have been injected with killed cultures. *In vitro* cultures manifest a distinct resistance to the action of solvents which readily dissolve the usual non-acid-fast bacteria. That this resistance is associated with acid-fastness seems likely (2). Concentrated acids or alkalies and pepsin-hydrochloric acid mixtures have been found to deprive tubercle bacilli of their acid-fastness and to cause their solution. The effect of other reagents which have been tried is less certain.

Löwenstein (3) was not able to confirm the work of Much, who found that solutions of lecithin and neurine caused loss of acid-fastness and granulation of the tubercle bacillus. According to Porter (4) glycerin extracts of various organs, when incubated with tubercle bacilli, cause them to lose their acid-fastness and to dissolve. The fat solvents such as chloroform, ether, absolute alcohol and benzol, and the lower members of the fatty acid series, such as formic, acetic, butyric and valerianic, have no effect on the morphology of the tubercle bacillus.

In testing the effect of some of the common oils and oil products on cultures of tubercle bacilli it was found that oleic acid produced profound changes in the morphology and staining of cultures dehydrated by means of alcohol. Two samples[2] of oleic acid which are presumably of different manufacture are alike in their behavior. A twenty-one day glycerin broth Erlenmeyer flask culture of a human type (H37[3]) tubercle bacillus is rapidly dehydrated. The flasks used for the cultures are of 100 cc. capacity and in three weeks a thin film of growth spreads over the entire surface of the broth. The growths of two flasks are combined by pouring one into the other before dehydration. To

[1] From the Department of Pathology, Washington University School of Medicine, St. Louis, Mo.

[2] One of the commercial oleic acids used was obtained from Merck and Co., New York City, and the other from the Henry Heil Chemical Co., St. Louis.

[3] A human type of tubercle bacillus from the Saranac Laboratory.

dehydrate, a sufficient amount of 95 per cent alcohol is added to the flask, to sediment the growth and at the end of one minute the liquid decanted. To the flask 50 cc. of 95 per cent alcohol are at once added and at the end of another minute the alcohol rapidly decanted and the flask drained for a few seconds. To the growth 10 cc. of oleic acid (*U. S. P. Merck*), containing two drops of distilled water suspended by vigorous shaking, are added, and the flask placed at 37°C.

At the end of one day many bacilli have become beaded, with bipolar staining predominating, and a greater number decolorize with acid-alcohol after staining with Ziehl-Neelsen solution. After several days in the incubator there remain only a limited number of acid-fast bacilli in heavy smears, which originally showed thousands per oil immersion field. A few acid-fast bacilli tend to persist. The amount of macroscopic growth is less after a week, and in six or eight weeks is greatly diminished, and consists chiefly of bacilli which have lost their acid-fastness, together with an occasional acid-fast one.

To make the stains, 2 or 3 loopfuls of the suspension are placed on a slide and a drop of xylol added. After spreading about with a platinum loop the xylol is evaporated over a flame, the slide being held in a slanting position to allow the oleic acid to accumulate at one end of the slide. The preparation is washed with xylol, and when dry it is stained by the Ziehl-Neelsen method. Care is necessary to prevent the xylol igniting. The treatment with xylol has no effect on the morphology or staining of the tubercle bacillus.

A conclusive explanation of the solvent action of the oleic acid has not been found. However, several factors which influence the solution have been determined. The possibility of oleic acid containing enzymes has been considered and a decrease in the solvent activity, which results from heating the oleic acid at 100° to 110°C. for one-half hour, at first suggested that this might be the explanation. The heat, however, drives off moisture and it has been noted that the addition of small amounts of water increases the solvent effect:

A twenty-one-day flask culture is rapidly dehydrated and to it there is added 10 cc. of oleic acid, which has been heated at 100° to 110°C. for thirty minutes in an open flask on an asbestos pad. After two-days' incubation there is no change in the bacilli. Two drops of water are added. Nine days after the addition of the water there is a granulation in some of the bacilli and some loss of acid-fastness but the effect of the oleic acid is much less than that of the unheated.

ACTION OF LIPASES ON CULTURES OF TUBERCLE BACILLI

The lipase of the castor bean has been brought into contact with cultures; but in aqueous solutions no effect on the tubercle bacillus has

been noted, and in combination with oleic acid it has not been found to increase the action of this acid:

A twenty-one-day Erlenmeyer flask culture is dehydrated and to it there is added 0.5 gm. Tanaka (5) lipase, ground in a mortar with 10 cc. of water. After one week of incubation there is no change in the bacilli. Also 0.5 gm. Tanaka lipase added directly to a culture is without effect.

When 0.5 gm. lipase is added to the oleic acid, solution progresses in the usual way. Efforts to secure solution by combining lipase with dilute emulsions of oleic acid have been ineffective. It may be added that attempts to secure solution by means of less concentrated solutions and emulsions of oleic acid have failed.

The experiments of Porter (4) have been repeated only with guinea pig liver and spleen; and a departure from his technique has been made, in that larger amounts of culture have been employed. The following experiment serves as an example of the results obtained:

To 20 gm. of fresh guinea pig liver are added 40 gm. of glycerin. The liver is crushed in a mortar, mixed with the glycerin and the mixture filtered through thin muslin after it has been subjected to two days incubation at 37°C. Two drops of toluene are added, to inhibit bacterial growth during incubation. To 5 cc. of the filtrate, 15 cc. of salt solution, one drop of toluene and a bit of culture a few millimetres across are added. At the end of one week there is no gross change in the culture and microscopically there is no conclusive evidence of solution.

INFLUENCE ON SOLUBILITY OF THE CHARACTER OF THE CULTURE

It has frequently been noted that actively growing cultures which have spread as a thin film over the entire surface of the medium dissolve more rapidly than old cultures or very young cultures:

A heavy forty-two-day culture, which has been in the refrigerator two months, is dehydrated in the usual way and 5 cc. of oleic acid added. At the end of one week there is much undissolved macroscopic growth, but microscopically there are abundant disintegration forms and many bacilli which are not acid-fast.

Cultures dehydrated for several hours with 95 per cent alcohol or with absolute alcohol are resistant to the action of the oleic acid:

A twenty-one-day growth (20 cc.) is decanted to a flask containing 500 cc. of 95 per cent alcohol. After 4½ hours the clear alcohol is decanted and 10 cc. oleic acid added. Most of the precipitate other than the bacilli appears to be dissolved by the oleic acid. At the end of one week the bacilli show little change.

Heat-killed cultures resist the action of the oleic acid:

A twenty-one-day culture, washed with salt solution, is desiccated and subjected to 100°C. for one hour in the dry-heat oven. After cooling, 5 cc. of oleic acid and one drop of water are added and mixed with the growth. After one week smears show no morphological changes in the bacilli.

Similar results are obtained with cultures subjected to moist-heat sterilization:

A twenty-one-day culture is heated in the Arnold sterilizer for one hour, dehydrated in the usual way and 5 cc. oleic acid together with one drop of water added. At the end of one week the bacilli are unchanged.

On the other hand, cultures killed by suspension in toluene water are acted upon by the oleic acid but the action appears to be less extensive:

A twenty-one-day culture is washed with salt solution, the salt solution decanted, and the growth covered with 20 cc. of distilled water, to which two drops of toluene have been added. After 24 hours at room temperature the toluene is decanted, the culture dehydrated in the usual way and 5 cc. oleic acid together with two drops of water added. At the end of twenty-four hours there are many granular forms and many bacilli which are not acid-fast. At the end of one week the amount of undissolved culture is much greater than when toluene is not used.

CONCLUSIONS

1. Preparations of oleic acid from two different commercial sources have manifested a profound effect on massive cultures of the tubercle bacillus rapidly dehydrated with alcohol. The changes in the morphology of the bacilli consist of the formation of granules and polar bodies and loss of acid-fastness with complete solution of many bacilli.

2. The maximum effect is exerted on living cultures. A diminished action has been noted on cultures killed by suspension in toluene water.

3. The experiments suggest the possibility but do not warrant the conclusion that the solvent action is due to a thermolabile enzyme contained in the tubercle bacillus acting only in the presence of undiluted oleic acid.

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TUBERCULOSIS IN ENGLAND AND WALES

A STATISTICAL ANALYSIS AND REVIEW

GODIAS J. DROLET[1]

In no country, perhaps, are vital statistics gathered so carefully as in England. A study of the last reports of the Ministry of Health and of the Registrar General will amply repay all students of the epidemiology of tuberculosis. The first gives nation-wide figures of the present morbidity from tuberculosis, and in the 1921 statistical review of the second can be seen a careful analysis of the mortality from this disease as far back as sixty years ago. Annual details of the mortality, all carefully standardized so as to permit proper comparisons, with reviews of the trend of tuberculosis throughout the last three-score years, are furnished in the Registrar's report.

During 1922, 69,259 new cases of tuberculosis were registered throughout England and Wales. Deaths from this cause claimed 42,777 victims. According to the postwar census of England and Wales, taken in 1921, the total population of the country now amounts to 37,885,000, of which slightly over 2,000,000 are in Wales.

MORBIDITY

Compulsory notification of tuberculosis in England and Wales requires the registration of both the pulmonary and nonpulmonary forms of the disease. In 1922, out of the total primary notifications of 69,259 cases of tuberculosis, 53,422 were of the pulmonary and 15,837 of the nonpulmonary type. These figures of recognized tuberculosis cases in England indicate a morbidity rate for the disease of 183 per 100,000 population during 1922. The details of new cases of tuberculosis found in England and Wales each year since 1915 are given in table 1.

[1] Statistical and Research Service, New York Tuberculosis Association.

599,417 DEATHS SINCE 1911

The tuberculosis death rate in England and Wales during 1922 was again 112 per 100,000, or practically the same as in the two preceding years of 1920 and 1921. The postwar decline has, therefore, for the present, been completely arrested. It should, however, probably be considered as a partial gain, if we recall the very large amount of unemployment which has been prevailing lately.

The death rate from pulmonary tuberculosis during 1922 was only 89 per 100,000, and that of other forms than pulmonary, 23 per 100,000. The death rate from tuberculosis in England and Wales during the past

TABLE 1

*England and Wales: Tuberculosis morbidity, 1915 to 1922 inclusive**

YEAR	"PRIMARY NOTIFICATIONS OF TUBERCULOSIS CASES" (NEW LIVING CASES REGISTERED)					
	Number of cases			Morbidity rate per 100,000		
	Pulmonary	Non-pulmonary	All forms	Pulmonary	Non-pulmonary	All forms
1915	68,309	22,283	**90,592**	193	63	**256**
1916	68,109	22,799	**90,908**	197	67	**264**
1917	68,801	20,884	**89,685**	204	62	**266**
1918	71,631	18,942	**90,573**	214	57	**271**
1919	61,154	16,357	**77,511**	166	45	**211**
1920	57,844	15,488	**73,332**	154	41	**195**
1921	56,334	15,368	**71,702**	149	40	**189**
1922	53,422	15,837	**69,259**	141	42	**183**

*Compiled from Reports, Ministry of Health and of the Registrar General of England and Wales, by G. J. Drolet, Statistician, New York Tuberculosis Association.

three years (around 112 as compared with the peak reached during the war, in 1918, of 192) represents a decrease of more than one-third, actually of 41 per cent; but, as compared with the prewar tuberculosis death rate in 1913 of 134, it shows a net decrease of only 16 per cent during the last ten years. Since 1911, up to 1922, inclusive, tuberculosis alone took 599,417 victims in England. Table 2 contains the annual details of tuberculosis mortality since 1911.

INCOMPLETENESS OF TUBERCULOSIS RETURNS IN ENGLAND

An obvious difference of practice in certifying causes of death and classifying them in England and Wales renders difficult a full appreciation of the ravages caused by tuberculosis in that country. As compared

with American practice, there is in England and Wales in the opinion of the writer an unusually large number of deaths allowed to remain unclassified as to primary cause among those included in the reports of the Registrar General as due to either acute or chronic bronchitis.

First: In 1922, in England, we see the proportion of deaths attributed to forms of tuberculosis other than pulmonary amounting to 21 per cent of the total, whereas in the United States Registration Area, during 1920, the proportion of this group of deaths was 15 per cent. The difference between the two may represent, in part, a greater amount of tuberculosis among children in England and Wales, owing to the lesser attention paid

TABLE 2

*England and Wales: Tuberculosis mortality, 1911 to 1922 inclusive**

YEAR	DEATHS FROM TUBERCULOSIS			STANDARDIZED DEATH RATE PER 100,000		
	Pulmonary	Other forms	All forms	Pulmonary	Other forms	All forms
1911	38,422	14,698	53,120	104	41	145
1912	37,269	12,782	50,051	99	37	136
1913	36,203	13,273	49,476	96	38	134
1914	37,838	12,460	50,298	99	36	135
1915†	40,803	13,492	54,295	116	39	155
1916†	40,769	13,089	53,858	123	39	162
1917†	42,335	13,599	55,934	138	42	180
1918†	45,338	12,735	58,073	152	40	192
1919	35,984	10,328	46,312	95	31	126
1920	32,791	9,754	42,545	84	29	113
1921	33,505	9,173	42,678	85	27	112
1922	33,919	8,858	42,777	89‡	23‡	112‡

*Compiled from Reports, Ministry of Health, and of the Registrar General of England and Wales, by G. J. Drolet, Statistician, New York Tuberculosis Association.

†Refers only to Civilian Population.

‡Provisional crude rate.

to the cleanliness and refrigeration of milk supplies, watched over so much more carefully in the United States; or else an incomplete accounting of all deaths due to phthisis.

Second: The number of certificates accepted in England and Wales by the Registrar General with bronchitis as the cause of death numbered 33,684 during 1922; in other words, they were even more numerous than those credited to pulmonary tuberculosis, which numbered during the same year only 33,505. The death rate credited to the first ill-defined group in England and Wales was 89 per 100,000 during 1922, the same as phthisis itself. During 1920, in the entire United States Registration

Area, with a population twice as great, the total deaths due to both acute and chronic bronchitis numbered only 11,609, furnishing a death rate of 13 per 100,000 as against the English rate of 89. New York City, with its location close to the ocean and its acknowledgedly very great humidity and dampness at certain seasons, had a death rate from bronchitis of only 9.5 in 1922.

Even with the more generally cloudy and humid character of the climate in England, and the inferior system of heating of houses (at least in the homes of the general population), both of which make for a greater amount of sickness from colds and bronchitis than in America, the writer is of the opinion that a large number of the deaths credited to bronchitis in that country are primarily due either to pneumonia, especially bronchopneumonia, or to tuberculosis itself, and that therefore the figures of tuberculosis in England and Wales are an understatement of the full ravages caused by that disease. When comparing the death rate from pulmonary tuberculosis in England and Wales with that of America, this difference in procedure should be remembered.

WAR PERIOD

The standardizing of the tuberculosis mortality in England and Wales brings out more fully the influence of the war in raising the tuberculosis death rate. The figures now available for that period are higher than those previously published. The increase in the last reports is due to the fact that the crude mortality rates previously reported for the civilian population during the war were based upon an abnormal population, naturally short of a very large number of men in military service, which by itself alone should have, under normal conditions, yielded instead a lower tuberculosis mortality. The redistribution of the civilian population during the war period to a standardized and comparable composition, as in normal times, furnishes a correction of the rate which shows more fully what actually happened. The corrected rates may be studied in table 2. As previously stated, a rise of 41 per cent occurred in 1918 over the 1913 mortality.

INFLUENZA EPIDEMIC

The theory that the recent influenza epidemic may have been responsible for the lower rates of tuberculosis after its visitation finds little support in the English returns according to the Registrar General. On this point he states that "the fact that the ground gained has been more than

maintained goes to show that the decline was not, in the main at all events, an exceptional after-effect of the great influenza epidemic resulting from the deaths in 1918 of pththisical patients who would otherwise have survived to swell the mortality. . . . . A further slight fall has occurred, instead of the rise to be expected if the cause of the previous fall had been of the nature suggested."

TUBERCULOSIS AMONG INFANTS

The infant mortality from tuberculosis in England and Wales has been falling steadily and to a greater extent, even, than that among adults. Sixty years ago, namely, during the five-year period of 1861 to 1865, the infant mortality from tuberculosis, or the number of deaths under one year of age per 1,000 births, was 9.29 for tuberculosis of all sites, whereas in 1921 it was only 1.54, a decrease of 84 per cent. The Registrar

TABLE 3

England and Wales: Standardized mortality from tuberculosis: 1851–1920

(Rate per 100,000 population)

PERIOD	PULMONARY			OTHER FORMS			ALL FORMS		
	Males	Females	Persons	Males	Females	Persons	Males	Females	Persons
1851–1860	269.4	285.4	277.2	78.3	62.9	70.6	347.7	348.3	347.8
1861–1870	261.2	257.8	259.0	74.5	59.9	67.3	335.7	317.7	326.3
1871–1880	235.9	211.9	223.1	72.1	58.2	65.1	308.0	270.1	288.2
1881–1890	196.6	167.2	181.0	69.0	57.9	63.4	265.6	225.1	244.4
1891–1900	163.3	122.6	141.8	65.2	55.4	60.3	228.5	178.0	202.1
1901–1910	135.8	95.1	114.3	53.3	47.3	50.3	189.1	142.4	164.6
1911–1920	130.6	86.8	107.6	39.9	34.2	37.0	170.5	121.0	144.6

General states that in England and Wales "the declines of mortality from pulmonary and from nonpulmonary tubercle have followed totally different courses. That from pulmonary tubercle has been declining since the commencement of the official record in 1838, and especially, at a remarkably constant rate, since 1866; while the rate from nonpulmonary changed but little from 1851 to 1891, but has since then fallen at an exceptionally rapid pace." The Registrar, besides questioning the correctness of the diagnosis of tuberculosis in children formerly, adds that of course "since the commencement of the century, infant mortality in general has declined enormously; second, that Koch's discovery must have greatly lessened the exposure of infants to infection by leading to their protection from infective sputum, and that the increase in institutional treatment of phthisis must have operated in the same direction."

MORTALITY SEVENTY YEARS AGO

In 1851 the mortality from all forms of tuberculosis, standardized for proper comparisons, was 357 per 100,000 persons then living. Pulmonary tuberculosis prevailed seventy years ago at a rate of 282. The mortality from tuberculosis during each decade since 1851 is indicated in table 3.

In England and Wales, during the decade of 1851 to 1860, the death rate from all forms of tuberculosis was 349 per 100,000 population of that period. The rate in both sexes was then practically equal; if anything,

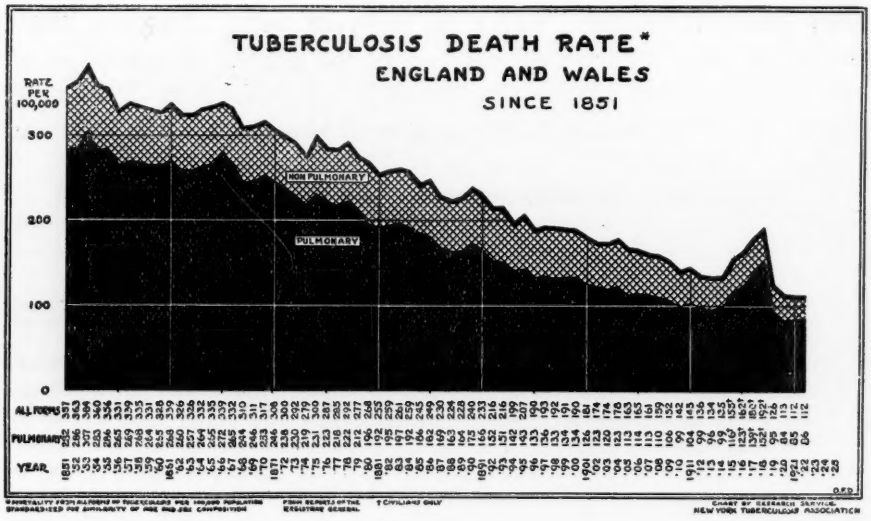

CHART 1

slightly higher among females. During the last decade of 1911 to 1920 the death rate among males was higher, namely 171, or 30 per cent higher than among females. During the six decades under consideration, the tuberculosis death rate for all forms of the disease declined by 51 per cent among males and by 65 per cent among females. The decline from pulmonary tuberculosis was higher than the decline from nonpulmonary forms, which averaged in the latter case 48 per cent. The death rate from pulmonary tuberculosis among females declined by 70 per cent.

RATE OF DECLINE ACCELERATING

The Registrar General's 1921 Report contains the results of a study of the annual mortality and of the rate of decline during all that period.

He notices the surprising constancy of the decline over so long a period—a constancy not in the rate of fall, but in the actual amount of fall. As a matter of fact, in England and Wales tuberculosis has shown (ignoring the abnormal war period) *a constantly accelerating rate of decline*. The importance of this acceleration in the rate of decline should be noted. It is an outstanding result which, in the opinion of Haven Emerson, should be expected to take place in the course of a disease of a communicable character when steadily brought under control.

ANTITUBERCULOSIS ORGANIZATION

Under the National Health Insurance Act a comprehensive and balanced number of schemes have been devised against tuberculosis in England and Wales, for development by local authorities. All of these are subject to and require the approval of the Minister of Health, so that measures may be fairly undertaken where most needed and only after study by experts.

On March 31, 1923, according to the report of the Minister of Health, the number of approved residential institutions for the treatment of tuberculosis, including both those provided by local authorities or by voluntary organizations, numbered 441, with a total of 19,386 beds available. There were 198 sanatoria throughout England, under the direction of both groups of organizations, of which 129 were provided for by local authorities and were, therefore, publicly supported, and 69 were supported by voluntary work. The total number of sanatorium beds available numbered 13,096. In addition, 61 institutions provided 3,310 beds for the treatment of tuberculosis in children. There were also 493 beds reserved for tuberculosis in 128 general hospitals. Finally, there are in England 2,287 beds provided by local authorities in special isolation hospitals. It is interesting to note that among public beds for tuberculosis there are 27 reserved in 8 dispensaries for the special observation of cases of tuberculosis, presumably those in which it is desired to clear a doubtful diagnosis.

For home or domiciliary treatment of tuberculosis, the number of approved dispensaries in England amounts to 442. There were in England, at the beginning of 1923, responsible and trained Tuberculosis Officers to the number of 341 in charge of local schemes for tuberculosis work.

The British Exchequer supplements the expenditures of local authorities for tuberculosis work to an amount almost equal to that expended by the local organizations. During the fiscal year 1922–1923, the Ministry of Health, under Parliament authority, made the following payments to local authorities in support of their expenditures on tuberculosis schemes: £1,185,421 for the treatment of insured persons and for the maintenance of antituberculosis work; £393,258 for the residential treatment of ex-service men, the latter sum including £22,501 for special re-training; and £14,832 for special services on behalf of ex-service men. For 1923–1924 the Government has asked Parliament to provide a total of £1,350,000 for similar purposes.

THE CHEMISTRY OF THE BLOOD IN TUBERCULOSIS[1]

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The work that has been done on the blood chemistry of tuberculosis is either old, involving antiquated methods, or it includes a few scattering observations on tuberculous subjects that chanced to be thrown in with other data on pathological material. Wells (1) calls attention to this fact. Study of the chemistry of the tubercle bacillus and tuberculous material seems to be far in advance of that on the blood in the disease. There are a few exceptions to this statement, and these have been signposts in pursuing the present study. From these scattering reports, in certain instances valuable clues have been obtained that have resulted in interesting findings.

The aim of this study was first, to ascertain from a chemical standpoint the actual conditions that exist in the blood in tuberculosis and second, equally important, to endeavor from such information to attempt to establish a logical and rational basis of tuberculosis therapy.

This can be only a brief and preliminary report. The various groups of subjects under investigation will be outlined and only some of the more important points in each will be touched upon, leaving the more detailed work until later.

There are certain advantages, however, in making a "composite" chemical blood picture that are not apparent in a study of individual chemical groups. Therefore, a partially composite study has been attempted on a small series of patients and will be reported here.

Our study embraces the following groups though not all will be reported on at this time:

Group 1: Clinical and clinical laboratory findings, such as cell count, color index, Arneth formula, basal metabolic rate and other information incident to the condition of the patient.

Group 2: Physical properties of the blood, including total volume, cell volume, specific gravity, freezing point depression, conductivity, viscosity, refractive index, total solids, ash and water balance.

[1] From the laboratory of the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

Group 3: Inorganic constituents, including calcium, magnesium, sodium, potassium, iron, chlorides, sulphates and phosphates.

Group 4: The distribution of the phosphorus-containing compounds.

Group 5: Nitrogen constituents.

Group 6: Non-nitrogenous constituents, such as sugar, acetone bodies, bile pigments, phenols and miscellaneous compounds not embodied in the above groups.

Group 7: Blood gasses, including alkali reserve and H-ion concentration of venous and arterial blood.

Group 8: Proteins of the plasma and the whole blood.

Group 9: Lipoids.

The above grouping and classification were decided upon because of their satisfactory application in the present study.

We have also departed from the usual clinical classification of tuberculosis. Aschoff's pathological classification has been combined with the National Tuberculosis Association or Turban-Gerhardt anatomic classification. This again is for convenience, and for the purpose of showing more clearly the results obtained, and is not offered as a substitute for existing systems, although activity more closely parallels the pathological than the anatomic concept.

It occurred to us, however, that a classification on a purely anatomic basis, or on the present N.T.A. classification, is not adequate to show true chemical differences. At least, it is only partially adequate. It cares for only one phase of the problem, that is, quantity, and does not take into consideration the varying grades of quality that may exist in different types of the disease. If we are to arrive at a chemical understanding of tuberculosis we must attempt to determine what there is in some individuals and races that render them resistant to the disease and, on the contrary, what causes certain other races and individuals to succumb rapidly. This can best be done by a study of the *quality* of the disease as well as the *quantity*. In the classification used here we have considered only two groups relating to quantity, namely, moderate and massive involvement. We have omitted the incipient group or those having slight involvement, because, in the first place, it is difficult to differentiate between this group and the early moderately advanced cases, it is difficult to ascertain from clinical records alone whether it is actually tuberculosis or not, and it is a type of disease that would be so slight that it is a question whether chemical differences would be manifest. Therefore, this group will be omitted for the

present. We have omitted the exudative type with moderate involvement, because patients do not remain long in this group and are therefore difficult to classify.

Therefore, we have rather arbitrarily classified the disease into six groups, combining Aschoff's, Romberg's and the National Tuberculosis Association's classifications as follows:

Group I includes patients having massive involvement, who are of exudative type.

Group II consists of patients having massive involvement but are holding their own. We have termed this a neutral group.

Group III is similar to *group II*. The involvement here is moderate.

Group IV is representative of those having moderate involvement with signs of improvement and proliferative changes.

Group V is of massive involvement with proliferative changes, including the chronic fibroid or cirrhotic type.

Group VI includes those with complications other than tuberculous.

METHODS

For the chemical examination and the metabolism test the patient was deprived of breakfast. The metabolism test was made before any exercise had been taken. The Boothby-Sanford apparatus was used throughout this work and in some cases a duplicate determination was made with the Sanborn apparatus.

The blood was drawn under sterile conditions in Keidel tubes containing either 2 mgm. of neutral sodium oxalate or 3 mgm. of hydrated sodium citrate per cubic centimetre of blood, or without an anticoagulant, depending upon the examination to be made. The data presented here were obtained by procedures selected, from various quantitative biological methods, for their accuracy and applicability. Some precautions have been previously reported (2) and other variations will be presented in subsequent papers. The value of the colorimeter and the nephelometer in a chemical study of the blood can be judged from the following: Colorimetric methods were used for the estimation of total nitrogen, nonprotein nitrogen, uric acid, urea nitrogen, creatinine, creatine, amino acid nitrogen, sugar, cholesterol, cholesterol esters, fibrin, globulin and albumen. Total phosphorus, lecithin phosphorus, acid-soluble phosphorus, inorganic phosphorus and fats were determined nephelometrically. Titration methods were employed for calcium and chlorides, while gravimetric methods were utilized for the estimation of specific gravity and total solids.

All of the nitrogen determinations, with the exception of total nitrogen, together with the sugar estimations, were made upon the Folin-Wu (3) filtrate,

which is prepared by deproteinizing whole blood with sodium tungstate and sulphuric acid. For the estimation of nonprotein nitrogen, urea, creatinine and creatine, the procedure has essentially been that of Folin and Wu (4). The total nitrogen of the blood was determined by the micro-Kjeldahl method. The amino acid nitrogen was determined by the colorimetric method of Folin (5), and the uric acid by the Benedict (6) procedure.

The calcium determinations were made upon plasma from citrated blood, using the technique of Kramer and Tisdall (7) as applied to serum. The method of Bloor, Pelkan and Allen (8) was employed for fatty acids and cholesterol, as well as the older method of Bloor (9) for cholesterol. The various forms of phosphorus were determined according to Bloor (10) and the cholesterol esters by the method of Bloor and Knudson (11). The chlorides were estimated according to Austin and Van Slyke (12), by titrating the excess of silver nitrate used to precipitate the chloride with potassium iodide, using starch as an indicator.

The reaction of phosphomolybdic acid with cuprous oxide, as developed by Folin and Wu (13), is the basis for the estimation of sugar. The plasma proteins were determined according to Wu (14).

The total solids represent the nonvolatile matter at 120°. The specific gravity was calculated from the weight of a known quantity of oxalated or citrated blood. Correction for the amount of anticoagulant used was applied in both the total solid and the specific gravity determinations.

With very few exceptions all determinations have been performed in duplicate and unless suitable checks were obtained the results were rejected. All precipitations of blood samples have been done within one hour of the drawing of blood. This has been done to preclude any change dependent on standing. The solutions after preparation were stored at 36°F. and all examinations were completed by the third day.

The proteins and total solids are expressed in percentages. All other results are given in mgm. per 100 cc. of blood. The chlorides are reported as sodium chlorides and the phosphorus as orthophosphoric acid.

EXPERIMENTAL

The data, presented in table 1, are given for the purpose of showing the general clinical condition of the patient in order that a more accurate interpretation may be placed upon the subsequent chemical findings. Certain points are in themselves interesting and instructive and will be dwelt upon briefly. The most noteworthy is the spirometric reading. We have found, as did Dreyer (15) and Myers (16), that the spirometric reading is a clinical test of first importance in tuberculosis and will give, in many instances, more reliable information,

when used with the constitutional symptoms, than the physical examination. Several patients, who were classified as *far advanced B*, gave spirometric readings little below normal, while other patients with the same classification would show lung destruction to the amount of 50 per cent. The seemingly inconsistent state of affairs lies in the fact that any cavitation detectable on physical examination places the patient in the far advanced group, although only a part of one lobe may be affected, while the spirometric reading will tell with a fair degree of approximation the amount of lung tissue involved. It is not intended to advocate the supplanting of physical diagnosis by the spirometer, but we consider it a valuable adjunct in gauging tissue involvement. For this work we have used the Sanborn spirometer with the accompanying tables of Dreyer. A point to be considered, however, is in the determination of the class to which the patient belongs. Most tuberculous patients belong to *Class C*, or the sedentary group, although no hard and fast rule can be used. Many patients who have recently been engaged in strenuous labor may belong to the *B* or *A* class.

The results on metabolism are practically in accord with McCann's findings (17), (18). The respiratory quotients ranged between 75 and 85 and the *B.M.R.* was always elevated by fever and coughing, but in reality such is not basal. One interesting observation is that the *B.M.R.* was -16.7 and -18.2 in two (*F.A.A.*) quiescent cases. This may be due to a general decrease in oxidation power of such individuals who have been affected for years by the toxemia of tuberculosis. Much parenchymatous degeneration may have practically deadened part of the body. A more plausible reason which certainly plays a partial rôle, however, appears to be the general habits of the individuals as a result of years of mental discipline. They have accustomed themselves to be in a passive state, in which the expenditure of energy is at a minimum.

The coagulation time, performed with a Bogg's apparatus, revealed nothing unusual. The Arneth formula was found in its customary relation to the disease, that is, higher in the exudative types. The leucocyte counts were about what one should expect. The high ratio of polymorphonuclears over lymphocytes indicates, no doubt, a certain degree of secondary infection in rapidly ulcerating tuberculous lesions, while the reverse may indicate less ulceration and more proliferation. There is a definite eosinophilopenia in severe tuberculosis.

GROUPS	INITIALS AND CASE NUMBER	SEX	AGE	PERCENTAGE OF NORMAL WEIGHT	RE : CELL COUNT	HEMOGLOBIN (DARE)	COLOR INDEX	VOLUME PERCENTAGE OF CELLS	CELL VOLUME $\times 10^{1}$	TRUE COLOR INDEX
					millions					
Group I.	M. Z. 15911	Male	37	75.5	6.6	90.0	0.75	40.0	60.0	0.89
	L. K. 9060	Male	33	72.0	4.0	75.0	0.96	29.7	74.2	1.3
	E. T. 16186	Male	20	88.0	5.45	70.0	0.71	39.8	73.0	0.97
	R. S. 14592	Female	24	79.0	4.13	80.0	1.0	31.8	77.0	1.3
	M. R. 16452	Female	17	80.0	4.74	70.0	0.78			
	F. U. 12623	Male	38	87.0	5.86	87.0	0.83	43.3	73.0	1.1
	H. G. 16227	Male	50	82.0	5.0	90.0	1.0	41.1	82.0	1.2
Average—Group I.				80.5	5.11	80.3	0.86	39.1	73.2	1.1
Group II. . . .	F. H. 16307	Male	37	82.0	4.99	62.0	0.69	34.5	69.8	1.0
	J. C. 16690	Male	24	86.7	4.16	84.0	1.12	37.4	90.0	1.2
	E. M. 2871	Male	25	80.0	5.08	90.0	1.0	40.5	89.0	0.9
	M. C. 13174	Male	32	100.0	4.66	80.0	0.94	41.5	89.0	0.9
	I. Z. 16550	Male	25		5.46	75.0	0.77	39.2	71.8	1.1
	J. S. 16293	Male	40	82.0	5.56	70.0	0.7			
Average—Group II.				86.1	4.97	76.8	0.87	40.6	81.9	1.0
Group III. . . .	E. B. 15724	Male	21	97.0	6.11	85.0	0.77	47.0	77.0	1.0
	P. 14829	Male	25	89.0	4.87	80.0	0.90	42.5	87.0	1.4
	H. O. 16278	Male	19	85.0	4.6	72.0	0.87	36.6	80.0	1.0
	T. S. 15443	Male	20	88.0	5.02	75.0	0.83	47.0	93.0	0.90
Average—Group III.				87.2	5.14	78.0	0.84	43.3	84.2	1.07
Group IV. . . .	B. K. 16528	Female	17	105.0	5.26	78.0	0.77			
	J. D. 15919	Male	32	95.0	6.09	90.0	0.82	42.5	70.0	1.1
	F. S. 16048	Male	33	95.0	6.00	81.0	0.75	47.0	78.0	0.96
	F. K. 12096	Female	19	94.0	4.30	80.0	0.99	38.2	90.0	1.1
Average—Group IV.				97.2	5.41	82.2	0.83	42.6	79.3	1.05
Group V.	F. H. 15602	Male	34	83.0	5.25					
	R. M.	Male	33	80.0	4.52	75.0	0.92	39.0	86.0	1.1
	T. H. 3511	Male	36	78.0	4.67	75.0	0.89	41.5	88.0	1.0
	W. S. 15770	Male	37		4.11	83.0	1.0			
Average—Group V.				80.3	4.64	77.6	0.94	40.2	87.0	1.1
Group VI. . . .	M. P. 16724	Female	19		3.80	55.0	0.77	25.6	67.0	1.1
	F. S. 16734	Female	18	80.0	4.67	60.0	0.68	30.5	65.0	1.0
	R. S. 16610	Female	33		3.42	62.0	0.82	28.0	82.0	1.0
Average—Group VI.				80.0	3.96	59.0	0.76	28.0	71.3	1.0

TAB
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LE 1
laboratory findings

TRUE COLOR INDEX	LEUCOCYTES	LEUCOCYTE RATIO $\frac{P}{L}$	EOSINPHILES	ARNETH'S INDEX	COAGULATION TIME	B.M.R.	VITAL CAPACITY	CLASSIFICATION AND REMARKS
					minutes			
0.89	19.4 M	6.5	3.0	80.0	8.3	+16.45 H +12.16 S	−45.7 C	F.A.C. Left-sided pneumothorax; rapidly failing.
1.3	11.6 M	3.4	0.3	89.0	8.5	−8.4 H +0.73 S	−53.0 C	F.A.C. Critically ill.
0.97	8.3 M	1.6	3.0	90.0	6.0		−61.2 C	F.A.B.
1.3	8.37 M	3.2	3.0	88.0	6.6		−20.49 C	F.A.C.
	17.7 M	5.9	1.0	88.0	3.6		−48.85 C	F.A.C.
1.1	10.1 M	3.0	1.0	72.0	4.5		−23.5 C	F.A.B.
1.2	10.0 M	5.4	6.0	74.0	6.5		−58.8 C	F.A.C.
1.1	12.2 M	4.1	2.5	83.0	6.3		−44.5 C	
1.0	14.0 M	3.9	3.0	79.5	5.5	+29.0 S +25.3 H	−28.5 C	F.A.B. Just holding his own
1.2	11.0 M	4.4		77.0		+14.4 H	−16.6 C	F.A.B. Just holding his own
0.9	13.9 M	8.6	1.3	78.8	5.2	+4.6 H	−63.72 C	F.A.B. Failing slightly; fibroid with tuberculous enteritis
0.9	10.4 M	3.6	0.7	83.0	5.9	+8.4 H	−67.8 C	F.A.B. Gaining slightly
1.1	12.5 M	2.8	1.7	62.0				F.A.A. Fair condition; gaining
	12.7 M	2.6	1.0	83.5	6.5		−3.3 C	F.A.B.
1.0	12.4 M	4.3	1.5	77.3	5.8		−35.9 C	
1.0	8.5 M	1.3	1.0	72.0	3.6		Normal C	M.A.B.
1.4	7.3 M	1.4	1.0	72.5	6.5		−38.4 C	M.A.B.
1.0	9.65 M	2.1			6.2		−39.0 C	M.A.B.
1.90	6.6 M	1.0	1.0	84.5	5.2		−12.1 C	M.A.B.
1.07	8.0 M	1.4	1.0	76.3	5.4		−29.8 C	
	11.15 M	3.2	2.0	70.0	7.0		Normal B	M.A.A.
1.1	10.9 M	1.2	4.7	68.0	6.0	−3.8 H −1.4 S	+14.6 A	M.A.B. Doing well
1.96	8.1 M	2.3	0.7	68.0	7.0	−5.0 H	+0.6 A	M.A.B. Doing well
1.1	7.4 M	4.2		78.0	6.7		−14.99 C	M.A.A.
1.05	9.4 M	2.7	2.5	71.0	6.8		0.07 C	
	5.14 M	1.8	3.0	75.0			−8.2 B	F.A.A.
1.1	10.2 M	3.5	1.3	68.0	10.0	−16.7 H	−27.4 C	F.A.A. Quiescent fibroid
1.0	9.3 M	1.6	1.3	55.5	7.6	−18.2 H	−33.8 C	F.A.A. Quiescent fibroid
	9.3 M	1.4	2.0	66.5	5.3		−5.9 C	F.A.B.
1.1	8.5 M	2.0	1.9	66.2	8.6		−18.8 C	
1.1	12.3 M	11.5		87.0	6.2			F.A.C. Died before completion; Wassermann, 4 plus
1.0	21.1 M	4.3	1.0		8.0	−17.5 H	−48.6 C	F.A.C. Very ill; Wassermann, 3 plus
1.0	20.4 M	8.5				+20.0 H		Hodgkin's disease producing Addison's syndrome; B.M.R. unsatisfactory
1.9	17.9 M	8.1	1.0	87.0	7.1		−48.6 C	

TABLE 2

Physical properties of blood in tuberculosis

INITIAL AND CASE NUMBER	SPECIFIC GRAVITY	NORMAL SPECIFIC GRAVITY (CALCULATED)	TOTAL SOLIDS	VOLUME PERCENTAGE OF CELLS	N.T.A. CLASSIFICATION
Group I					
H. G. 16227	1.055	1.055	20.4	41.1	F.A.C.
E. T. 16186	1.060	1.054	19.8	39.8	F.A.B.
F. U. 12623	1.056	1.055	20.6	43.2	F.A.B.
M. Z. 15911	1.043	1.055	19.0	40.0	F.A.C. Pneumothorax, one side
R. S.	1.050	1.045	17.3	31.8	F.A.C.
Average—Group I....	1.053	1.053	19.4	39.2	
Group II					
M. C. 13174	1.056	1.055	20.8	41.5	F.A.B.
E. M. 2871	1.054	1.054	20.4	40.5	F.A.B.
J. S. 6293	1.055	1.053	20.2	37.9	F.A.B.
Average—Group II....	1.055	1.054	20.5	39.9	
Group III					
H. O. 16278	1.051	1.051	19.1	36.6	M.A.B.
P. 14829	1.066	1.056	21.1	42.5	M.A.B.
E. B. 15724	1.062	1.058	22.3	47.2	M.A.B.
Average—Group III..	1.059	1.055	20.8	42.1	
Group IV					
F. K. 12096	1.051	1.052	19.3	38.2	M.A.A.
W. S. 15770	1.058	1.056	22.7	44.2	F.A.B.
Average—Group IV...	1.054	1.054	21.0	41.2	
Group V					
M. G. 4466	1.058	1.055	20.0	39.6	F.A.B. Hemorrhage case
F. H. 15602	1.059	1.058	21.6	47.0	F.A.A.
Average—Group V....	1.058	1.056	20.8	43.3	
Group VI					
M. P. 16724	1.041	1.046	13.6	25.6	F.A.C.
S. E. 14653	1.057	1.056	21.4	42.5	F.A.B.
Average—Group VI...	1.049	1.051	17.5	34.0	

The red cell counts were also below normal in the extremely ill patients or those who had massive involvement, although quiescent. The hemoglobin (Dare) was usually depressed, with the cell count indicating a secondary anemia. Only a few had a color index of 1 or over. These points have been mentioned by Riedel (19). The total volume of the red cells, determined by Sundstroem and Bloor's modification of the hematocrit methods (20), decreases in the same order as the cell count, so that we should expect the individual cell volume to remain constant. This did not occur; the individual cell volume was usually decreased, indicating a greater proportion of reduction of total cell volume than inversely in the number of red cells. The cell volume is determined by dividing the total cell volume per cubic millimetre by the number of red cells. This result is then multiplied by 10 to the ninth power in order to make it appear in the table as a whole number. From this result and the color index of each cell a value may be obtained which we have called the *true color index*. This is merely the color intensity or index for a unit volume of cell instead of a unit number. In some instances, with massive involvement and severe constitutional symptoms, there is an increase of this color intensity per unit volume of red cell.

The weight is expressed as percentage of the normal according to height-weight charts. This method of course is not always reliable, but there is no more reliable gauge of the patient's condition than the weight curve, and it is too frequently neglected. Taken with the temperature, pulse and spirometric reading, it affords a means *par excellence* by which a patient can be taught to gauge his own condition.

Relative to physical properties of the blood (table 2), we shall report only a few of our findings. In general, the specific gravity is lower in emaciated and anaemic patients and, as anticipated, total solids usually parallel the specific gravity. The total red cell volume, however, appears to have the greatest effect on specific gravity. For example, M.P., in *group VI*, who had practically a normal plasma protein content, which would give a specific gravity of about 1.03, has a whole blood specific gravity of 1.041, half way between the plasma specific gravity and the normal whole blood specific gravity. The total cell volume is only 25 per cent or almost half the normal. Therefore, the decrease parallels the decrease in red cell volume. The same proportional decrease occurs in the total solids. The many other factors and qualities that have a bearing on these changes will be discussed in the detailed reports

to follow, in which viscosity, refractive index, surface tension, water balance, etc., will be presented. The diurnal water variation described by Meyer-Bisch (21) would not enter into our results, because the specimens were drawn in the morning when the toxic effect of the auto-

TABLE 3*

Calcium content of blood of tuberculous patients

INITIAL AND CASE NUMBER	CALCIUM OF PLASMA	PERCENTAGE OF CELLS	CALCIUM OF WHOLE BLOOD	PERCENTAGE OF NORMAL CONCENTRATION IN PLASMA	COAGULATION TIME	N.T.A. CLASSIFICATION
			Group I (7 patients)			
					minutes	
Average—Group I.....	10.49		6.59	86.0	5.9	
			Group II (5 patients)			
Average—Group II.....	11.04		6.60	92.0	5.5	
			Group III			
P. 14829	11.40	42.5	6.55	94.0	6.5	M.A.B.
			Group IV (2 patients)			
Average—Group IV.....	11.57		6.36	96.5	6.5	
			Group V			
F. Z. 16380	10.15	37.5	6.43	84.0	7.0	F.A.C. Hemorrhage case
M. G. 4466	10.40	39.6	6.24	86.0	8.5	F.A.B. Hemorrhage case
K. B. 11619	9.60	35.8	6.17	80.0	5.0	F.A.B. Hemorrhage case
L. B. 16407	10.60	38.0	6.57	88.0	7.0	F.A.B. Hemorrhage case
R. M.	6.27	39.0	3.82	52.0	10.0	F.A.B. Fibroid; quiescent
Average—Group V.....	9.40		5.84	78.0	7.5	

* Whenever it has been possible to condense these tables, by taking the averages of several figures, this has been done. Wherever there has been individual variation, however, and such averages would not be representative, the detailed figures have been retained.

tuberculin is at its minimum and the water increase is therefore not manifest until the day advances.

Of the inorganic constituents only calcium, phosphorus and chlorides will be dealt with in this report.

The blood of tuberculous patients did not reveal any constancy regarding the relation of blood calcium content and stage of the disease

(table 3). By calculating the calcium in the whole blood, on the assumption that none exists in the cells as reported by Kramer (22), we find that the concentration per unit amount of plasma is less in a group of hemorrhage cases than in ordinary tuberculosis. This difference is not great and may be of no significance. One quiescent fibroid (R.M.), who had only 3.82 mgm. calcium per 100 cc. whole blood, had the rather long coagulation time of ten minutes. These results are quite in harmony with Maver and Wells's (23), in which they determined that the body calcium in guinea pigs was not subject to much fluctuation. Even after the injection of calcium the content soon reaches normal quantities.

In the table on nitrogen determination (table 4) we have included the chlorides and sugar results whenever estimations were made. We have performed several hundred of each, and have found definitely that the sugar content of the blood has no relation to tuberculous disease when this is not complicated by alimentary glycosuria. There is no reason to doubt, however, that the toxemia of the disease does not cause a lowered sugar tolerance and a tendency to alimentary glycosuria, as reported by Langston (24).

The results on chlorides have not been wholly in accord with those of Boenheim (25) who found the chlorides to decrease in proportion to the severity of the disease. Our results reveal the fact that chlorides are relatively constant and always above normal. If there is retention due to kidney disease, the chlorides are markedly increased. The chlorides never decrease below a certain limit, which we have found to be 410 mgm. per 100 cc. of blood (usually 430 mgm.). An important observation that appears to be rather constant, *when no serious kidney lesions occur*, is that chlorides and total nitrogen play a reciprocal rôle. When one is elevated the other is depressed. This may be one of the body's means of maintaining the requisite osmotic pressure between the tissues and the blood stream. Therefore, we have not found a decrease in chlorides in proportion to the severity of the disease, but an increase up to the terminal stage, when a slight decrease has occurred in a few instances. One patient (M.P., no. 7024) does not belong in *group I* because she had a complication of diabetes. This would cause a decrease of the average chlorides and an increase of average sugar values. The average far-advanced patient has a chloride content of 490 mgm. per 100 cc. of blood, while the average normal is around 460 mgm. per 100 cc. These figures have been established on several hundred analyses.

TABLE 4

Blood nitrogen in tuberculosis

INITIALS AND CASE NUMBER	CHLORIDES	TOTAL N OF WHOLE BLOOD	SUGAR	NON-PROTEIN N	UREA N	URIC ACID	PREP. CREATININE	TOTAL CREATININE	CREATININE BY DIFFERENCE	AMINO N	RESIDUAL N	N.T.A. CLASSIFICATION
Group I												
M. Z. 13911		2780		28.2	10.4	2.8	1.48	4.1	2.62	7.0	8.86	F.A.C. Critical
L. K. 9060		2500		27.6	15.6	1.8	1.0	3.0	2.0	4.8	6.4	F.A.C.
M. P. 7024	(430)	3145	(200.0)	23.2	13.2	3.4	1.5	5.1	3.6	6.0	2.4	F.A.B. Diabetic
A. P. 15768	475	3500	85.0	26.2	13.2	3.8	2.0	5.7	3.7	6.4	4.7	F.A.C.
G. H. 15793	500	3670	92.0	38.5	15.6	4.6	1.7	5.2	3.5	6.5	15.1	F.A.C.
M. R. 16452	495	2670		20.0	10.0	2.9	1.3	4.6	3.3	6.6	3.0	F.A.C.
Average—Group I.....	496	3044	88.5	27.2	13.0	3.2	1.5	3.6	3.10	6.2	8.4	
Group II (9 patients)												
Average—Group II.....	481.7	3135	90.4	31.6	12.5	3.5	1.6	4.7	3.1	6.3	11.3	
Group III (11 patients)												
Average—Group III.....	474.0	3265	92.8	30.1	14.8	4.1	1.8	5.3	3.5	6.7	8.3	
Group IV (6 patients)												
Average—Group IV.....	442.5	3461	83.6	32.8	14.3	3.90	1.8	4.4	2.6	5.7	9.5	

Group V												
R. M.		2800		31.8	11.0	4.0	1.8	5.7	3.9	7.3	11.8	F.A.A.
T. H. 3511		3400		29.0	10.0	4.3	1.5	5.0	3.5	6.2	11.0	F.A.A.
J. S. 11825	495	3390		24.0	10.3	3.4	1.5	4.4	2.9	6.4	8.6	F.A.Q.
Average—Group V.....	495	3177		28.3	10.4	3.9	1.7	5.0	3.4	6.7	10.5	
Group VI												
F. S. 16734		2650		26.8	10.6	3.5	1.4	6.0	4.6	7.3	7.4	F.A.C. Wassermann, 3 plus
R. S. 16610	495	2280	80.5	15.5	7.0	1.6	1.4	5.7	4.3	7.0	0.6	Hodgkin's; died
E. W. 834624 C.C.H.	490	1330		44.0	28.1	2.1	1.4	5.0	3.6	8.8	0.0	Rheumatic fever
H. B. 834716 C.C.H.	450	2120		38.8	15.5	3.6	1.5	4.8	3.3	8.3	13.3	Rheumatism
D. R. 834689 C.C.H.	440	2130		31.9	19.0	1.8	1.6	4.9	3.3	6.8	5.0	Chronic nephritis
A. P. 834636 C.C.H.	530	1250		39.2	10.0	4.4	1.5	5.8	4.3	7.3	19.5	Chronic nephritis
H. M. 835870 C.C.H.	530	1840		42.8	23.4	4.7	2.0	4.8	2.8	7.7	9.9	Chronic diffuse nephritis
Average—Group VI.....	489.2	1943	80.5	34.1	16.2	3.10	1.5	5.3	3.7	7.6	9.3	
Group VII												
R. C. B.	465	3220		39.9	14.7	4.3	1.5	4.7	3.2	8.5	14.8	Normal
A. M. P.	465	3260		29.8	13.9	4.0	1.3	5.1	3.8	7.2	6.9	Normal
L. A.	455	3620		29.0	10.5	2.5	1.4	4.8	3.4	6.2	11.0	Normal
Average—Group VII.....	461.7	3367		32.9	13.3	3.60	1.4	4.9	3.5	7.3	10.90	

The total nitrogen decreases in proportion to the severity of the disease, and fairly closely parallels the degree of anemia, specific gravity and total solids. In the moderately advanced proliferative types the total nitrogen is even above normal, conforming to Moraczewski's figures (26). This may be harmonized with the findings of Meyer-Bisch (21) and Petersen (27). As the disease becomes more exudative more "auto-tuberculin" is liberated, and the body cells and endothelium become overstimulated, with a resulting cellular fatigue and dehydration of body tissues and a slight dilution of the blood. In spite of the fact that diuresis is more marked, more water is evidently consumed and retained. On the other hand a slight amount of involvement or an improving condition will cause a slight stimulation, followed by a decrease in permeability, resulting in an increased water retention and a concentration of the blood solids.

The urea, uric acid and nonprotein nitrogen, as well as the residual nitrogen, are all depressed slightly in the severe cases and elevated above normal in the mid-groups. This is in harmony with the total nitrogen findings. Severe kidney involvement causes an actual retention of these various elements. Whether the increase in the milder cases is due to blood concentration or retention is not yet settled. It seems to be more probably due to blood concentration. The creatinine or, perhaps, more properly, "picrate-reducing substances," is lower in the extremely ill patients and higher in the moderately ill than normal. The question as to the occurrence of creatinine in the blood, at least in quantities usually assumed, has been raised by Behre and Benedict (28), upon the assumption that the so called creatinine content does not behave in the same manner as does added creatinine. For this reason the "creatinine" content has been referred to as "picrate-reducing substances." Raphael and Eldridge's (29) explanation of the creatinine curve in urinary findings may apply equally well to blood findings. They state that there is at first an increase in creatinine due to increased katabolism, then a decrease when the disease has reduced the muscle volume beyond a point where even normal figures cannot be maintained during the increased katabolism of tuberculosis. The amino acid nitrogen does not vary from normal, except in extremely ill patients, when it may be low, and in cases of retention when it is high.

In a study of the phosphorus partition (table 5) there are certain definite conclusions, while others are not so obvious. The lecithin phosphorus (phospholipins) is uniformly low in proportion to the exuda-

tive type of disease. As proliferation increases the lecithin phosphorus increases. This point will be mentioned again when lipoids are discussed. Henning (30) found quite normal figures for lecithin in tuberculosis. Our results are not what might be called abnormal, but each group, according to the type of disease, has a definite general average that is characteristic. The lecithin results were not so consistently low in far advanced exudative cases as is the cholesterol. This may help to account for the anemia in this type of case, because of the loss of the inhibiting action of free cholesterol on hemolysis. Neilson and Wheelon (31), however, found an increase to saponin resistance in tuberculosis. According to our results, this can only occur in the proliferative type of case, with the reverse process occurring in the exudative type. By calculating on the basis of Bloor's figures (24) for normal content of phosphorus in cells and plasma, we have tabulated, side by side, the theoretical result based upon the cell content and also the results that we obtained. This scheme has many advantages. It shows clearly that the acid-soluble phosphorus is more concentrated in the cells of patients having severe anemia, as the calculated figures were lower in these instances than the actual results, indicating that the decrease in cell volume did not proportionally decrease the phosphorus. In less severe cases the calculated results were generally equal to or slightly higher than the results found. While the acid-soluble phosphorus was more concentrated in the cells, it was still slightly lower than the normal, indicating that the phosphorus level was not maintained in advanced patients. The inorganic phosphorus was low in some severe cases but it was equally low in certain favorable ones. No conclusions can therefore be drawn from our figures regarding this fraction.

The results on "total phosphorus" and "lecithin plus acid-soluble phosphorus" vary only as the various constituents which have been described. There is a calculated fraction derived by subtracting the "acid-soluble plus lecithin" phosphorus from the total phosphorus that is interesting and may be of importance, although our figures are more or less erratic. A more careful study may reveal some important relation to cell destruction. In this group would fall nucleoproteins, which are not acid-soluble and are thrown out by the alcohol-ether precipitation. In a few gravely ill patients high results were obtained for this group, although certain "improving" cases were also high. This deserves more study, however.

TABLE 5

Distribution of phosphates in blood of tuberculous patients

INITIALS AND CASE NUMBER	ACID-SOLUBLE PHOSPHORUS		LECITHIN P		INORGANIC P		LECITHIN + ACID-SOLUBLE		TOTAL P		UNDETERMINED P		PERCENTAGE CELLS	CLASSIFICATION
	Calculated	Found	Calculated	Found	Calculated	Found	Calculated	Found	Calculated	Found	Calculated	Found		
Group I														
L. K. 9060	63.1	82.8	32.4	29.5	11.6	8.7	95.5	112.3	96.1	130.9	0.6	18.6	29.7	F.A.B.
D. B. 14452	59.0	61.2	33.4	28.1	12.4	9.6	92.4	89.3	93.0	112.0	0.6	22.7	26.7	F.A.C.
M. Z. 15911	80.8	80.8	36.0	24.3	12.7	11.9	116.8	105.1	118.4	106.6	1.6	1.5		F.A.C.
Average—Group I.....	67.6	74.9	33.9	27.3	12.2	10.0	68.2	102.2	102.2	116.5	0.9	14.3	27.7	
Group II														
I. Z. 16550	81.5	71.6	36.1	22.7	12.7	15.9	117.6	94.3	118.4	95.1	0.8	0.8	40.0	F.A.C.
F. H. 16304	72.6	86.8	34.3	26.7	12.2	12.0	106.9	113.5	107.6	118.6	0.7	5.1	34.5	F.A.B.
J. C. 16690	76.8	70.6	35.1	22.3	12.3	15.9	111.9	92.9	112.7	100.0	0.8	7.1	37.4	F.A.B.
W. 16744	82.2	59.1	37.5	35.1	13.0	9.2	119.7	94.2	121.3	113.0	1.6	18.8	40.0	F.A.B.
E. M. 2871	82.3	81.5	36.2	29.0	12.7	13.3	118.5	110.5	119.5	112.5	1.0	2.0	40.5	F.A.B.
M. C. 13174	84.1	70.0	36.5	27.4	12.8	11.2	120.6	97.4	121.6	99.1	1.0	24.2	41.5	F.A.B.
Average—Group II.....	79.9	73.3	35.9	27.2	12.6	12.9	115.9	100.5	117.0	106.3	1.0	9.7	39.0	
Group III														
T. S. 15443	93.9	70.6	37.5	33.8	13.4	10.3	131.4	104.4	133.5	124.6	2.1	20.3	47.0	M.A.B.
Group IV														
F. S. 16048	93.9	89.7	37.5	35.2	13.4	7.6	131.4	124.9	133.5	147.0	2.1	22.1	47.0	M.A.A.
J. D. 15919	85.9	78.2	36.9	36.4	12.9	5.8	122.8	114.6	123.8	137.0	1.0	22.4	42.5	M.A.A.
Average—Group IV.....	89.9	83.9	37.2	35.8	13.1	6.7	127.0	119.7	128.6	142.0	1.5	22.2	44.8	

Group V														
R. M.	81.5	79.9	36.1	47.5	12.7	11.1	117.6	127.4	118.4	136.8	0.8	9.4	39.0	F.A. Quiescent; fibroid
T. H. 3511	83.9	80.1	36.5	44.4	13.0	12.6	120.4	124.5	126.6	130.2	1.2	5.7	41.5	F.A. Quiescent; fibroid
L. B. 16407	78.8	58.9	36.9	33.1	12.8	10.3	115.7	92.0	116.6	116.0	0.9	24.0	38.0	F.A.B.
K. B. 11619	74.9	54.6	36.2	40.3	12.6	9.2	111.1	94.9	112.3	121.8	1.2	26.9	35.8	F.A.B.
Average—Group V.....	79.8	68.4	36.6	41.3	12.8	10.8	116.2	104.7	118.5	126.2	1.02	16.5	38.6	
Group VI														
M. P. 16724	56.0	58.4	32.8	24.1	13.2	13.3	88.8	82.5	89.4	108.7	0.6	26.2	25.6	F.A.C. Wassermann 4 plus
F. S. 16734	64.8	87.3	34.4	34.5	12.5	12.7	99.2	122.8	100.0	126.8	0.8	5.0	30.0	F.A.C. Wassermann 3 plus
M. L. DIsp. 10361	78.7	65.7	37.0	38.8	13.7	6.7	115.7	104.5	117.5	107.9	1.8	3.4	38.2	
Average—Group VI.....	66.5	70.6	34.7	32.5	13.1	10.9	101.2	102.9	102.3	114.5	1.06	11.5	31.3	

TABLE 6

Plasma blood proteins

INITIALS AND CASE NUMBER	DATE	ALBUMEN	GLOBULIN	FIBRIN	TOTAL PROTEIN	PROTEIN QUOTIENT $\frac{A}{G}$	PERCENTAGE GLOBULIN PROTEINS	PERCENTAGE FIBRIN GLOBULINS	RATIO X	N.T.A CLASSIFICATION	REMARKS
Group I											
M. Z. 13911	May 3	3.66	2.66	0.536	6.32	1.3	42.0	20.0	2.1	F.A.C.	Failing. Left-sided pneumothorax
M. R. 16452	May 23	1.71	4.10	0.082	5.81	0.4	70.0	2.0	35.0	F.A.C.	Failing
D. B. 14452	May 24	3.54	1.76	0.368	5.30	2.0	33.0	20.0	1.6	F.A.C.	Died. Hemorrhage case
F. Z. 16380	May 28	3.83	2.10	0.453	5.92	1.8	35.0	21.0	1.7	F.A.C.	Hemorrhage case
O. G. 12093	June 14	3.24	2.37	0.266	5.61	1.3	42.0	11.0	4.0	F.A.C.	Fibroid that gradually failed; died
B. W. 14577	May 27	3.24	2.66	0.312	5.90	1.2	44.0	12.0	3.7	F.A.C.	Died
Average—Group I.....		3.20	2.61	0.336	5.79	1.3	44.3	14.3	8.0		
Group II (9 patients)											
Average—Group II.....		4.22	1.62	0.398	5.84	2.8	27.5	27.3	1.3		
Group III (4 patients)											
Average—Group III.....		3.57	1.8	0.309	5.76	1.9	30.2	20.0	1.9		
Group IV (8 patients)											
Average—Group IV.....		4.32	1.75	0.234	6.08	2.6	28.7	12.9	2.4		

Group V											
R. M.	May 14	2.18	3.28	0.516	5.46	0.6	60	15	4.0	F.A.A.	Fibroid; quiescent
T. H.	May 14	3.28	3.59	0.309	6.87	0.9	52	8.0	6.3	F.A.A.	Fibroid; quiescent
L. B. 16407	May 24	3.77	2.47	0.242	6.24	1.5	40	10	4.0	F.A.B.	Hemorrhage case
M. G. 4466	May 28	3.66	2.56	0.407	6.31	1.4	40	15	2.6	F.A.B.	Fibroid; hemorrhage case
Average—Group V.....		3.22	2.97	0.368	6.22	1.10	47.5	12.0	4.2		
Group VI											
F. S. 16734	May 14	3.42	4.72	0.634	8.14	0.8	58	13	4.4	F.A.C.	Failing; 3 plus Wassermann
M. L. 10361	May 18	4.96	1.83	0.429	6.79	2.6	24	23	1.0		Suspected Hodgkin's
S. E. 14653	May 21	5.84	1.05	0.329	6.89	5.5	15	30	0.5	F.A.B.	Holding own; contracted lues; being treated
M. P. 16724	May 21	4.28	1.60	0.035	5.88	2.6	27	2	13.0	F.A.C.	Died; 4 plus Wassermann
G. J.	April 26	3.71	2.36	0.215	6.07	1.5	40	9	4.4		Double mitral lesion
R. S.		2.0	0.9	Trace	2.9						Hodgkin's with Addison's syndrome
Average—Group VI.....		4.03	2.08	0.274	6.11	2.6	32.8	15.4	4.7		
Group VII											
F. B.	April 25	3.73	1.49	0.282	5.22	2.5	28	20	1.4		Normal
J. T.	April 25	3.86	2.38	0.256	6.24	1.6	38	18	2.7		Normal
A. P.	April 27	3.10	2.18	0.232	5.28	1.4	41	10	4.0		Normal
L. A.	April 27	4.67	1.53	0.180	6.20	3.0	25	12	2.1		Normal
Average—Group VII.....		3.84	1.89	0.237	5.73	2.12	33.0	15.0	2.5		

The plasma proteins, tabulated in table 6, harmonize fairly well with results reported previously. Gram (32) made a study of fibrinogen content, and found that active tuberculosis gave high results; Levinson (33) had similar findings. In our work these statements are not wholly confirmed, for we have found "terminal cases" having extremely low results (M.R., no. 16452, a result of 0.082 per cent, and M. P., no. 16724, with 0.035 per cent).

The relation of albumen to globulin was found to corroborate Hurwitz and Meyer's (34) experimental findings in rabbits and Adler's (35) in human tuberculosis. That is, there is a general increase of globulin with corresponding decrease in albumen, as the disease advances. In

TABLE 7

Repeated examinations for plasma proteins in tuberculosis

INITIALS AND CASE NUMBER	DATE	FIBRIN	ALBUMEN	GLOBULIN	TOTAL PROTEIN	CONDITION OF PATIENT
S. E.	June 6, 1922	0.287	3.58	2.53	6.11	F.A.B.
14653	May 21, 1923	0.329	5.84	1.05	6.89	Contracted lues; treated
B. K.	April 2, 1923		2.59	2.17	4.76	Inc. B.; good condition; gaining rapidly; excellent condition
16528	May 23, 1923	0.103	5.18	1.39	6.57	
M. R.	April 2, 1923	0.320	2.59	1.02	3.61	Failing; F.A.C.
16452	May 23, 1923	0.082	1.71	4.10	5.81	Critically ill
H. V.	January 11, 1923		3.66	1.22	4.88	F.A.B.
16090	May 23, 1923	0.230	4.25	1.25	5.50	Losing slightly

other words, the "protein quotient" decreases. Therefore, taking these results with those of Gram, Levinson and others, it would indicate a parallel increase of fibrin, together with the other globulins, as the disease advances. These changes, however, did not always occur in the patients that we examined. For example, in M.R., no. 16452, *group I*, there was a high total globulin (4.10 per cent) with a low fibrin (0.082 per cent), while in S.E., no. 14653, *group VI*, there was a total globulin of 1.05 per cent with 0.329 per cent fibrin. The latter patient contracted syphilis and was treated prior to this change. This is shown in table 7. Peters (36) found more or less indeterminate results, among which were the following: If the globulin suddenly falls without a corresponding fall in albumen the prognosis is not so good as in cases

when both fall together; if both stay high the prognosis is bad. Two fatal cases (D. B., no. 14452, and M. P., no. 16724) in our series conform to the first class, and one nearly fatal case fits the third class (F. S., no. 16734). There appears to be a variety of changes that

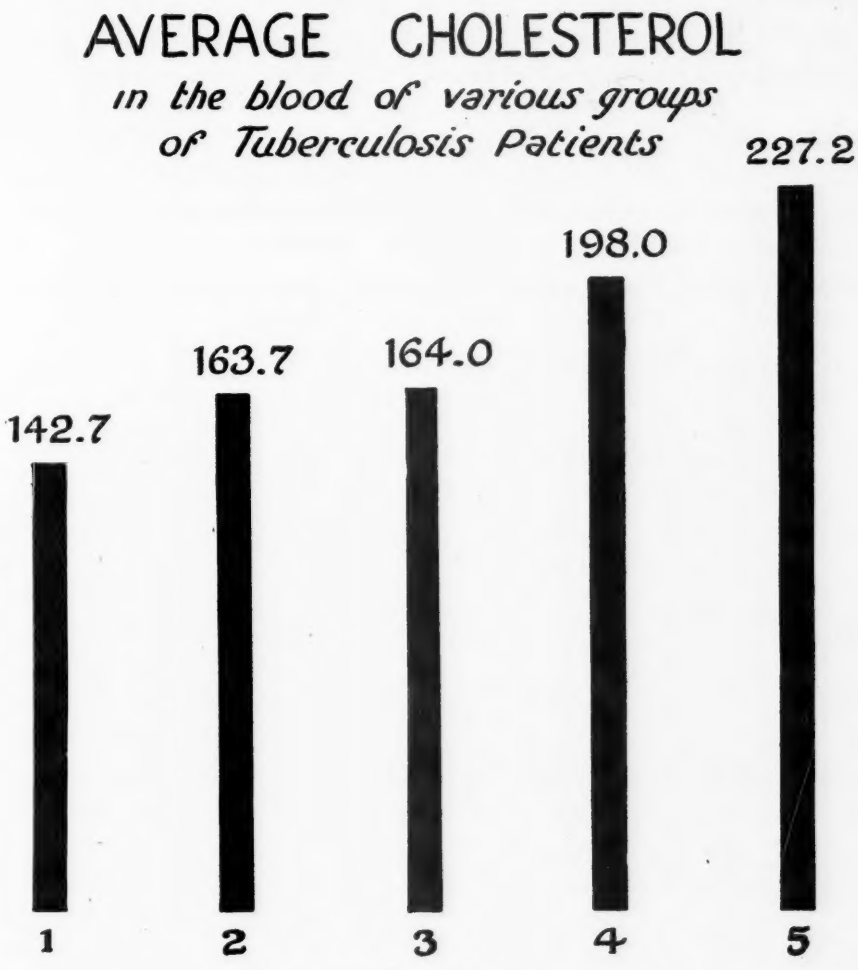

CHART 1

occur in the protein of tuberculous patients that are not yet understood and that need further study. The total proteins were generally increased in the midstages of the disease, and rarely were they below the normal except in certain terminal cases. This is essentially what Meyer-Bisch (21) found. In repeated examinations (table 7) on four

TABLE 8

Cholesterol in the blood of various groups of tuberculous patients

GROUP I		GROUP II		GROUP III		GROUP IV		GROUP V	
A. P. 15768	128.0	H. R. 15830	177.0	C. K. 15764	142.0	W. W. 16286	166.0	U. S. 15770	200
F. L. 15914	166.6	W. B. 15704	166.0	J. R. 15732	196.0	T. N. 16287	192.0	T. H. 3511	272
J. H. 15795	138.0	J. S. 16293	140.0	S. M. 15868	151.0	J. D. 15999	176.0	L. B. 16407	181.5
		P. R. 16041	150.0	J. H. 15817	200.0	E. K. 16202	202.0	C. B. 11619	180.0
E. T. 16186	152.0	E. S. 15803	180.0	L. A. 15912	169.0	E. G. 16216	227.0	R. M.	347.0
M. T. 15911	139.0	J. K. 15669	190.0	J. R. 15707	151.0	P. W. 15355	208.0	M. G. 4466	215.0
		F. H. 16304	144.0	M. N.	166.0	T. B. 16356	202.0	G. B. 1566	195.0
R. S.	149.0	J. C. 16690	133.0	J. L. 15668	166.0	F. S. 16040	214.0		
D. B. 14452	127.0	E. M. 2871	151.0	A. C. 15991	148.0				
O. G. 12093	125.0	M. C. 13174	143.0	W. L. 15599	168.0				
M. N. 16313	133.0	I. T. 16550	171.0	E. B. 15724	156.0	O. E. 14724	166.0		
F. S. 15915	135.0	G. D. 15248	180.0	T. S. 15543	155.0				
L. B. 16184	153.0	J. N. 16386	192.0	L. B.	180.0				
F. L. 16380	168.0	M. W. 16744	175.0	C. P. 14829	151.0				
L. K. 9060	142.0			H. O. 16278	163.0				
Average...	142.7		163.7		164.0		198.0		227.2

patients, within varying periods of time, some interesting figures were obtained. Plasma proteins are subject to sudden and marked fluctuations. S. E., no. 14653, has been mentioned previously. B. K., no. 16528, showed a shift from globulin to albumen and a gain in albumen on improvement. M. R. gave the reverse figures on failing. These figures are difficult to harmonize with those of Peter's and with the three patients mentioned above. More study is needed on this phase of the problem.

By far the most interesting and, we hope, the most valuable results from this work are those derived from a study of the lipoids (lipins). We were able to confirm the findings of Bachmeister and Hennes (37), and especially Weltmann (38), who report on the decrease of cholesterol in the exudative type of disease. The latter uses it as a prognostic

TABLE 9

Repeated cholesterol examination at an interval of 4 months

INITIAL AND CASE NUMBER	JANUARY, 1923	3 TO 5 MONTHS LATER	CONDITION OF PATIENTS
E. B. 15724	156	176	Gaining; M.A.B.
F. H. 15602	166	178	Gaining; fibroid; F.A.A.
J. D. 15919	163	176	Gaining; M.A.B.
J. S. 16293	140	161	Holding own; F.A.B.
H. R. 15830	166	177	Holding own; F.A.B.
F. W. 10988	170	158	Losing; F.A.B.
H. G. 16227	204	170	Losing rapidly; F.A.B.
W. S. 15770	201	193	Losing gradually; F.A.B.
M. Z. 13911	166	139	Critically ill; F.A.C.

factor. We have been able to confirm these findings as is shown in table 8 and chart 1. Furthermore, in far advanced quiescent patients the cholesterol is markedly increased and roughly proportional to the involvement.

Rosenthal and Petrzak (39), while studying tuberculosis following war malnutrition, attributed the decreased resistance in the former to low lipoid content. Table 9 illustrates beautifully the relation of the disease to cholesterol content. It is not so much the content that must be considered, but whether the content is rising or falling. Most tuberculosis patients give cholesterol results within normal limits. In the ones in which the values are rising we have invariably found an improving condition and in those in which they were falling the patient's condition became worse. Chart 2, of E. T., is a typical illustration of

this point. In January the weight was normal and the blood cholesterol was 185 mgm. per 100 cc. of blood. In February two analyses were made within two weeks of each other; both were over 200 mgm. per 100 cc. of blood. The weight likewise rose to 4 kilos above normal. In April, however, the weight dropped to 3 kilos below normal and the blood cholesterol dropped to 152 mgm. per 100 cc. of blood, and the clinical signs all became aggravated in proportion. The temperature went from 98°–99.5° to 100°–103°; the pulse, sputum and other signs became more marked.

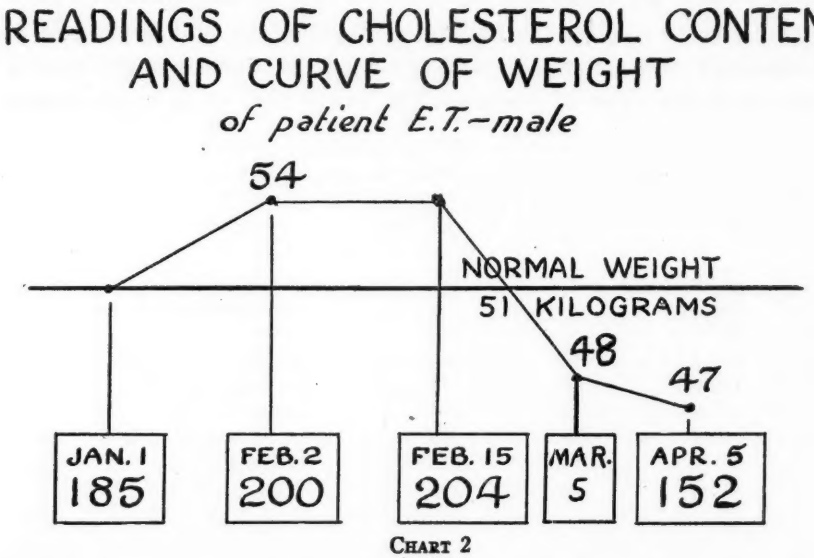

CHART 2

The relation, however, of cholesterol esters to the disease was not so satisfactorily determined. Results on the few specimens analyzed indicated that they were increased in proportion to the severity of the process, averaging in the exudative cases from 40 to 60 per cent against a normal of 33 per cent (Bloor). We did not verify the results of v. Eisler and Laub (40) who found the ester content decreased in severe tuberculosis. Only two very ill patients were thus found below normal in our series. In one far advanced quiescent patient (T. H., no. 3311) we found practically the total cholesterol content of the plasma in the form of esters, while there was only a slight amount of esters in the cell. In R. M., another similar type of case, we found a more nearly normal plasma ester content with none in the cells. In F. S., no. 16734,

a rapidly failing patient, a very similar relation prevailed except that the percentage of esters was higher.

Table 10 reveals these findings. There must be further study before any definite conclusions can be drawn from the cholesterol-ester content or ratio to free cholesterol.

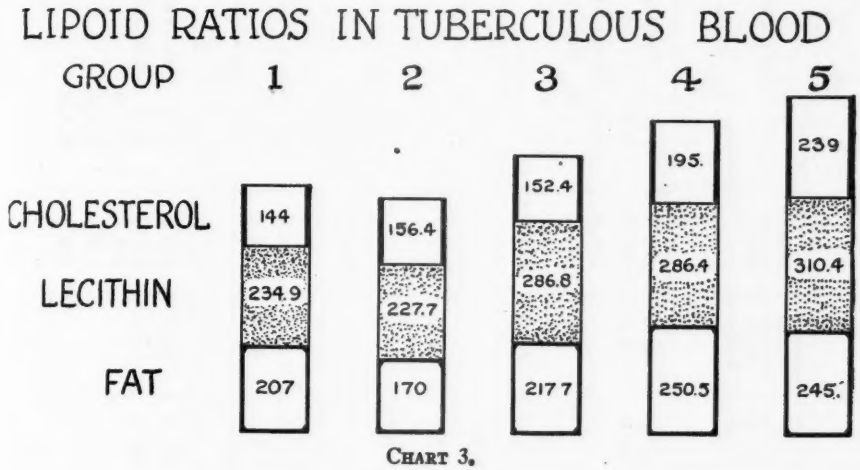

CHART 3.

TABLE 10

The partition of cholesterol and cholesterol esters between cells and plasma

INITIAL AND CASE NUMBER	TOTAL	ESTERS	FREE	ESTERS IN PLASMA OF 100 CC. BLOOD (CALCULATED)	ESTERS IN CELLS (CALCULATED)	PERCENTAGE OF CELLS	DIAGNOSIS
T. H.	Pl. 305	302	3	176.6	24.0	41.5	F.A.Q.; fibroid
3511	WB 272	200	72				
F. S.	Pl. 190	127.0	63.0	88.4	−4.0	30.5	F.A.C.; terminal
16734	WB 194	84.4	109.6				case
R. M.	Pl. 416	181.4	234.6	110.6	−6.0	39.0	F.A.Q.; fibroid
	WB 347.2	104.6	242.6				

The lecithin was previously discussed under phosphorus, but its relation to cholesterol and fatty acids is presented in chart 3. While there is not the characteristic increase, as in cholesterol, the fat and lecithin rise and fall parallel those of cholesterol, as Henning (30) has previously found. We were unable to corroborate Henning's results on cholesterol content by the saponification method. A slight decrease, which averaged about 12 mgm. per 100 cc. of blood, was consistently

TABLE 11
Lipoids

INITIALS AND CASE NUMBER	FATS, WHOLE BLOOD	CHOLESTEROL, WHOLE BLOOD: NONSAPONIFICATION METHOD	CHOLESTEROL, WHOLE BLOOD; SAPONIFICATION METHOD	DIFFERENCE BETWEEN THE TWO METHODS	CHOLESTEROL ESTERS; WHOLE BLOOD	PERCENTAGE OF CHOLESTEROL ESTERS	LECITHIN; WHOLE BLOOD	N.T.A. CLASSIFICATION
Group I								
M. Z. 13911	170.6	139.0	132.0	7.0	67.6	48.6	194.4	F.A.C. Pneumothorax, one side
L. K. 9060	221.0	142.0	135.0	7.0	40.5	28.6	230.0	F.A.
D. B. 14452	204.0	127.5	111.7	15.8			224.8	F.A. Terminal
F. Z. 16380	233.9	168.7					290.4	F.A.B. Hemorrhage
Average—Group I.....	207.4	144.3	126.2	9.9	54.0	38.6	234.9	
Group II (7 patients)								
Average—Group II.....	170.4	156.4	140.0	12.9	77.1	60.3	227.7	
Group III (2 patients)								
Average—Group III.....	217.7	152.5	149.5	6.0			286.8	
Group IV (2 patients)								
Average—Group IV.....	250.5	195.0	164.5	30.5	80.6	46.4	286.4	
Group V								
R. M.	315.0	347.2	304.8	42.4	104.6	30.0	380.0	F.A. Quiescent; fibroid
T. H. 3511	282.0	271.7	243.5	28.2	207.0	74.0	355.2	F.A. Quiescent
L. B. 16407	195.0	181.5	155.1	26.4			264.8	F.A.B.
K. B. 11619	199.0	180.0	155.2	24.8			322.4	F.A.B.
M. G. 4466	233.9	215.0					229.6	F.A.B.
Average—Group V.....	245.0	239.0	214.6	30.4	155.8	52.0	310.4	

Group VI

F. S. 16734	335.0	194.0	172.0	22.0	84.4	43.5	276.0	F.A. Wassermann 4 plus
S. E. 14653	199.0	216.0	126.6	58.6				
M. P. 16724	165.0	85.7			17.2	20.4	192.8	F.A.C.
R. S.	160.0	105.0					100.0	Hodgkins
Average—Group VII.....	214.8	150.2	149.3	40.3		31.9	189.6	

obtained by the saponification method over the nonsaponification method, but no results comparable to those of Henning's were ever obtained.

DISCUSSION

Not only a detailed knowledge, but also a composite view of this whole field of work, is necessary, in order to obtain the proper understanding and to draw the correct conclusions. We must consider the underlying causes for the various changes found and determine, if possible, the changes that are favorable and those that are unfavorable. We must also attempt to ascertain whether certain abnormal findings are the cause of certain results or are results of a certain cause. By such methods of procedure we shall arrive at a true understanding of tuberculosis and ultimately shall be able to control it in the living body.

Our results have demonstrated certain favorable signs in healing tuberculosis, as well as unfavorable signs in the exudative types. Most of our findings have been demonstrated previously, but certain ones we have emphasized in a more definite manner, while others are entirely new, so far as we are able to ascertain.

Some of the unfavorable signs observed in a study of the clinical and laboratory findings have been mentioned before and are household words amongst clinicians. In general, they seem to be brought about by a toxemia. A high Arneth's index, low red cell count, low hemoglobin and lymphocytosis are usually caused by a cell destruction due presumably to toxins. Just what these toxins are is problematical. Whether there are substances like Ruppels "tuberculinic acid" (41) or Vaughan's split products" from tissue destruction, they seem to destroy red cells and leucocytes, causing a secondary anemia, a relative lymphocytosis (as well as a true one) and a "shift to the left" in Arneth's index. In favorably progressing patients this destruction stops, and the tissues are allowed to function more normally. Owing to the fact that cholesterol parallels the improvement and increases in proportion to the involved tissue during improvement, it is certainly intimately involved in the process of healing in tuberculosis. Cholesterol has been known to neutralize the hemolytic action of saponin on red blood cells (Wells (42)). It may have a similar action on tuberculotoxin. It may act as a "tampon," to absorb such toxins and render them harmless. Just how this would take place is merely speculative. There must be some fundamental property in body cells to make and main-

tain adequate lipoid content and on this factor may rest the success or failure of the patient. It is not unreasonable to suppose that the lipoidal content is a healing measure instead of an accidental occurrence or purposeless result. It is surely worthy of exploiting therapeutically. First of all, the infection must occur, then the battle rages between the microbe and the host, then comes a time when the body cells are able to throw in healing factors, slight at first, and more as the healing continues. Whether these lipoidal substances are used for the neutralization of the toxins, for the extermination of the parasite or for the stimulation of the body cells to more proliferation, or all combined, is immaterial, so long as we know what the substance is and can duplicate the body's method. It seems quite plausible to attribute part of the action, at least, to the "toxin-neutralizing" action of these defensive agents. When the tubercles are forming and destruction is going on at a rapid rate, there is nothing that could possibly aid in inhibiting the process more than a neutralization of the toxins. This would permit the body cells to function more normally, would permit the cells in close proximity to the foci of infection to remain more normal and to resist death and autolysis, as well as the further spread of the bacilli. The reaction would then remain more localized, and the round and epithelioid cell blocking could develop to better advantage, followed by a growth of fibroblasts and connective tissue.

These favorable influences must only manifest themselves in a slight degree at the beginning of the progressive changes. In every instance these changes seem to be gradual, yet consistent. It appears to be necessary for the body cells and fluids to acquire, establish and maintain an ever increasing content or power to produce these substances. If these conditions could be reproduced artificially it would seem logical to expect that desirable chemotherapeutic measures could be established.

The argument may be raised that the increased cholesterol content is due to pus from cavities, but the content is only high in far advanced healing cases and not far advanced exudative ones, where the most pus exists; besides, the fat and lecithin rise with the cholesterol.

It does not seem unreasonable, therefore, to attribute a great many of the changes in the blood of tuberculosis to a "toxin and tampon" action of the tuberculoproteins and the lipoids. There are certain exceptions in our series. For example, M. Z., no. 15911, had a red cell count of over six million and hemoglobin of 90 per cent, yet he was

critically ill and should have had marked anemia because of the amount of involvement. This patient had a left-sided pneumothorax, which will account for these findings. Lippert (43) found that pneumothorax caused a depression of oxygen in arterial blood, and increase in carbon dioxide and a compenatory increase in hemoglobin and red cells. He stated that the oxygen content drops suddenly and markedly after pneumothorax and that cell regeneration is necessary to endow the greatest O_2 carrying power possible to the blood. Many patients do not survive this readjustment.

Just what effect such a toxemia will have on physical and chemical properties of the blood is problematical. The chloride retention may be due partially to such action. In spite of the fact that Boenheim (25) states that there is a general depression of chlorides in severe tuberculosis, he also states that there may be some urinary retention in severe cases without kidney involvement. In febrile tuberculosis, a high chloride content may be expected because of the same condition in other fevers. This retention may be one of the body's methods to prevent evaporation through the decrease in aqueous tension; by a change in the permeability of the cells or a change in the colloids within the cell. We previously stated that in the moderate involvements there was usually an increase of specific gravity, total solids, etc., in other words, an increased concentration of substances in the blood.

It was noted that, in a rough manner, a certain relation existed between total nitrogen and chlorides. The chloride content, though never below normal, was relatively lower when the nitrogen was high and vice versa. This relation is believed to be occasioned by the fact that there is an increase of both total nitrogen and chlorides in moderately advanced stages, though the nitrogen increases more rapidly than do the chlorides. During the far advanced stages, the nitrogen content falls while the chloride content continues to rise. Except in terminal cases, the chloride content appears to remain high.

SUMMARY

The blood chemistry of tuberculosis has been studied on a large series of patients, of which about 25 were done completely in order to obtain a composite picture of the blood constituents in this disease. The work was divided into nine parts for convenience and a preliminary report given on the whole. For the sake of simplicity, tuberculosis

patients were classed as exudative, neutral and proliferative, each with moderate and massive involvement, instead of according to the usual National Tuberculosis Association classification.

In the clinical examinations 12 metabolism determinations were reported out of a series of about 50. The respiratory coefficient was found between 75 and 85, and the B.M.R. was usually positive and in proportion to the activity, ranging from 10 to 30 per cent above normal, while quiescent patients, especially fibroids of long standing, were 15 to 20 per cent below normal.

Spirometric readings were also found to be a good measure of the patient's lung destruction, being more accurate in this respect than the clinical examination.

Blood counts were found to be about the same as have been reported previously. There is a high Arneth's index, the coagulation time is only slightly increased, leucocytes are markedly increased, eosinophiles decreased, and there is an increase of polymorphonuclears over lymphocytes in the more exudative patients. The color index was found over 1 in several patients, thus slightly simulating pernicious anaemia. A figure called the "true color index" was derived from the color index, whereby the color of a unit volume of red cell was calculated. This reveals the fact that the increase of color index is exaggerated in tuberculosis because the cells are smaller. The cell volume is about three-fourths normal in the average tuberculosis patient and appears to be slightly less in proportion to the severity.

In physical properties, the specific gravity and total solids decrease in severe cases and increase in moderate cases. In general, the actual specific gravity parallels the calculated figure.

Calcium figures were about normal in all stages. Six hemorrhage patients gave slightly lower percentage calcium in the plasma than other tuberculosis patients.

Total nitrogen is high in moderate involvement and low in advanced stages. Chlorides generally increase to the terminal stage, when a slight decrease occurs. There is, roughly, a reciprocal relation between total nitrogen and chlorides in the early stages.

Sugar varies, but it has no relation to the stage of this disease if there be no complication of alimentary glycosuria.

"Creatinine" is increased in moderate involvement, but decreases when the patient becomes emaciated. Other nitrogen compounds vary roughly as the total nitrogen.

Of the phosphates, the lecithin phosphorus is decreased and the acid-soluble phosphorus increased in severe cases. The lecithin continues to rise as improvement advances.

Of the proteins, the fibrin and globulin are usually increased together, with the severity of the disease. The total proteins and albumen are likewise decreased. Plasma proteins are subject to sudden and marked changes in quality and quantity. Many variations render the results slightly uncertain.

Cholesterol decreases in proportion to the severity of the disease and is of definite prognostic aid. It also rises in proportion to the improvement and this increase is in proportion to the lung destruction. The cholesterol esters are not constant, although, in general, they are high in advanced patients and may be low in fatal ones.

The fats and lecithin roughly parallel the rise and fall of cholesterol.

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SOME RESULTS OF ARTIFICIAL PNEUMOTHORAX TREATMENT[1]

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Artificial pneumothorax has won for itself an accepted place in the treatment of tuberculosis. Suggested in principle in the works of Hippocrates, according to Krause (1), as a possible treatment of adhesive pleuritis when this condition was associated with a wound or incision for empyema, its institution as a practical treatment is usually credited to Forlanini, who reported his first cases in 1894. In the past decade it has enjoyed widespread popularity and its literature has accumulated rapidly to vast proportions. There have arisen, on the one hand, a feeling of pessimism as to its essential usefulness and, on the other, a tendency to constantly extend the accepted indications for its employment. It is only by a careful study of results over an extended time that a balanced judgment in the matter can be attained.

Pneumothorax treatment has been employed at Gaylord Farm Sanatorium in rather a desultory way since 1912; but it has been only within the last two years that any considerable number of cases has been under treatment at the same time. The present study has been undertaken in search of a guide to the more careful selection of proper cases, and my only excuse for adding to the large body of literature is to put on record a few statistical findings of ultimate results obtained in our early cases, and to point out, if possible, the causes for the better results which we seem to be obtaining with our present series.

Since the opening of the Sanatorium 75 cases have been selected for artificial pneumothorax, in which time about 2900 patients have been under treatment; or 2.6 per cent of patients have been so treated, a very conservative selection, as 5 per cent has come to be generally accepted as the usual proportion of cases found suitable for such treatment. Of these 75, it was found impossible to produce collapse in 13.

[1] From the Gaylord Farm Sanatorium, Wallingford, Connecticut.

As it was our impression before beginning the study that our recent series of cases was proving much more satisfactory, the cases are divided into two series: (1) those prior to June 1920, comprising 37 cases of pneumothorax and 6 unsuccessful attempts, and (2) the later cases, 25 successes and 7 failures.

A comparison of results obtained in the two series is shown in the first four tables: ***immediate result*** meaning the condition of the patient on discharge; and ***ultimate result*** the patient's condition at the present time, as determined by our follow-up statistics.

TABLE 1

Series 1: 37 cases

Immediate result (condition on discharge)

6 far advanced, 30 moderately advanced, 1 lung abscess

	per cent
Improved (symptomatic relief)	10 or 27
Unimproved	23 or 62.2
Progressive	1 or 2.7
Died	3 or 8.1

TABLE 2

Ultimate result

	per cent
Improved	1 or 2.7
Cured	2 or 5.4
Died	30 or 81.1
No record	4 or 10.8

Of the 30 dead, 1 lived over 5 years, 4 over 2 years, 8 over 1 year, 8 from 6 to 12 months, 7 under 6 months, 1 died a few hours after treatment from hemoptysis, and 1 died, time unknown. Four of this 30 died from causes other than tuberculosis. Of this series only 2 are able to support themselves under ordinary conditions of life in apparent good health. The patient tabulated as improved is still unable to resume his former occupation.

There is a very noticeable improvement in the immediate results seen in a comparison of tables 1 and 3. A comparison of ultimate results is of course impossible as 52 per cent of the second series are still under treatment. It is perhaps pertinent to point out that all of the 13 still under treatment show marked general improvement. Of those patients listed as improved in table 4, one whose treatment was carried on for just a

year has been employed at the Sanatorium as storekeeper, a position involving considerable moderately severe manual labor, and has been working regularly, six to eight hours a day for the last eighteen months. Another whose treatment lasted for seven months has been working regularly in charge of the Sanatorium office for about the same length of time as the first, averaging about six hours a day. Of the other 4, three are continuing the cure in other environment, and from recent reports are showing steady improvement; and one is still a bed patient at home,

TABLE 3

Series 2

Immediate results in 25 more recent cases

7 far advanced, 17 moderately advanced, 1 minimal

	per cent
Improved	20 or 80
Unimproved	5 or 20

TABLE 4

Late results (25 cases)

	per cent
Under treatment (all improved)	13 or 52
Treatment discontinued	12 or 48
Died	3 or 12
Improved	6 or 24
Arrested	2 or 8
Unimproved	1 or 4

his condition but little improved. The two listed as arrested have been able to support themselves for over a year on full time work under ordinary living conditions. Two of the patients still under treatment are supporting themselves under ordinary home conditions by doing part time work.

The report of 81.1 per cent dead in the first series of 37 cases is undoubtedly discouraging, but in partial explanation of this report several facts have to be considered. In the time period covered, 1912 to 1920, pneumothorax treatment was in its infancy, and the realization of the necessity for long-continued treatment wanting; the indication for collapse was conceived as considerably more narrow, comprising only the very ill and most frequently being employed as a last resort measure; and the technique was decidedly inferior to that now employed.

In series 1, 21 cases or 66.7 per cent were kept up for less than two months, 7 cases or 18.9 per cent from two to four months, 5 cases or 13.5

per cent from four to six months, 2 cases or 5.4 per cent from six to twelve months, and only 2 cases for over a year. In series 2, of 25 cases, on the other hand, treatment has been kept up for over two years in 3, over one year in 9, and over six months in 5.

To determine the influence of duration of treatment the entire 62 patients were grouped according to the time interval.

TABLE 5

Effect of duration of treatment on results

	UNDER 2 MONTHS	2 TO 4 MONTHS	4 TO 6 MONTHS	6 TO 12 MONTHS	1 YEAR
Immediate results					
Number of patients	24	10	7	7	14
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
Died	12.5	0	0	0	0
Unimproved	66.6	70	57.1	14.2	0
Improved	20.8	20	42.8	85.8	100
Ultimate results					
Number of patients	24	10	7	7	14
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
Died	70.8	70	57.1	42.8	14.2
Unimproved	4.1	10	0	0	0
Improved	4.1	0	0	42.8	21.4
Cured	4.1	10	14.2	0	7.1
Under treatment	4.1	10	14.2	14.2	57.1
Unknown	12.5	0	14.2	0	0

The indications for treatment in our series have conformed fairly closely to the generally accepted standard, being divisible into the following general groups:

1. Moderately advanced patients, whose lesion is either entirely confined to one lung, or in whom the lesion of the contralateral lung is apparently inactive and does not extend over more area than that portion of the lung above the second chondrosternal articulation. This group is almost always given a trial on the usual regimen of rest treatment and only on failure to make a decided improvement is pneumothorax instituted. We include also in this group certain minimal cases, who after a fair trial on the rest regimen fail to rid themselves of signs of activity and whose X-ray picture shows a spreading lesion.

2. Moderately advanced or far advanced patients with chronic type of lesion usually associated with cavity formation. Here treatment may be undertaken on the more active lung even in the face of considerable trouble

in the other side, in the hope of ameliorating symptoms and getting the patient up and around.

3. Severe or repeated hemoptysis, without a very marked lesion on the other side, provided that the side from which the hemoptysis is occurring can be definitely determined.

4. Very acute unilateral lesion, where X-ray shows a dense mottling confined to one lung. Our feeling here is that collapse should be induced without delay.

In series 1, 18 cases or 48.6 per cent showed physical signs of involvement in the untreated lung to about the second rib, while 12 cases or 32.4 per cent showed no trouble on the opposite side. In series 2, 14 cases showed no signs in the untreated lung while in 7 cases there was a slight involvement of the untreated side, in no case of extent below the second rib. Pneumothorax was given as a last hope three times in series 1 and once in series 2, for hemoptysis 7 times in series 1 and 5 times in series 2; and given in series 1 once for each of the following indications,—to keep up spontaneous pneumothorax, for pleurisy with effusion and for lung abscess.

TABLE 6

COMPLICATIONS	SERIES 1	SERIES 2
	per cent	*per cent*
Pleurisy with effusion	7 or 18.9	8 or 32
Pleuritis pain	19 or 51.3	10 or 40
Spread to other side	7 or 18.9	3 or 12
Subcutaneous emphysema	9 or 24.3	2 or 8
Fatal hemorrhage	1	0
Dyspnea, very marked	2	0
Pulmonary edema	1	0
No symptoms recorded	5 or 13.5	10 or 40

COMPLICATIONS

An improvement in technique is indicated in a comparison of the complications arising in the two series (table 6).

The technique employed at Gaylord Farm for the induction of pneumothorax resembles, in most particulars, that in general use elsewhere, and has been modified but little since the treatment was first used. Nitrogen has been the gas of choice, as we feel that it is somewhat less rapidly absorbed than atmospheric air. An instrument of the Robinson type, slightly modified, has been employed and has proved entirely satisfactory. The manometer scale has recently been modified to read in millimetres

of mercury. In the earlier series a rather large cannula needle (Brauer-Floyd-Robinson type) was used, while in the later series a simple needle of smaller calibre (antitoxin $1\frac{1}{2}$, no. 21, B & D) has been employed. All usual aseptic precautions are observed and a sterile cotton filter introduced in the rubber connection leading to the needle. In series 1 a somewhat larger average dose was given, positive pressures being frequently obtained, while in the later series we are using smaller doses, ranging from 250 to 800 cc., given at more frequent intervals, two to four weeks, and avoiding in almost all cases the production of positive pressure. Thus, in our later series we have a larger proportion of partial collapse cases than in the earlier series, 60 per cent against 48.6 per cent in the first series.

The low incidence of pleurisy with effusion in the first series is probably accounted for by the much less frequent use of the X-ray in diagnosis, as in three of the eight cases recorded in series 2 the effusion was so small and temporary, that it was recognized only by X-ray examination.

STUDY OF UNSUCCESSFUL ATTEMPTS

Of the 13 unsuccessful attempts at pneumothorax induction, 6 fell in the first group, making 13.9 per cent of failures; the other 7 in the later group making the high figure of 28 per cent, which means that over one-quarter of the cases attempted in this time proved a failure. Of the 13, 9 were classified as Moderately Advanced and 4 as Far Advanced.

The indication for treatment was about the same as in the more successful group, for the most part progressive lesions which failed to improve under an ordinary rest regimen. The condition of the untreated lung was no signs in 5 cases; few signs, doubtful or no râles in 5 cases; signs of moderate activity in small part of the untreated lung in 3.

The immediate results obtained were:

Discharged as improved	4
Discharged as unimproved	2
Discharged as progressive	7

The ultimate results:

Died	7
Improved	2
Not known	3

Of the 7 dead, 1 lived over five years, 1 over two years, 1 over one year, 3 over six months and 1 died in five months.

The reason for failure seems in every case to be directly attributable to pleural adhesions, so widespread as to make the introduction of gas into the pleural cavity impossible. In 4 cases no manometric readings could be obtained, despite numerous punctures in various locations. In 5, slight negative pressures were obtained, with small variations, which changed promptly to a positive pressure on the introduction of small amounts of gas. Three cases were interesting, in that a positive pressure of +2 or +3 mm. Hg. was obtained with small variations, this positive pressure gradually falling to 0 while under observation, and in one case even to −1. On slowly introducing gas the pressure became slightly increased, but again fell on waiting. On one case slight negative pressure with good variations became strongly positive on the introduction of gas, to fall again to slightly negative. In this manner 250 cc. were slowly introduced. In all of these cases X-ray failed to reveal any collapse, in spite of the apparent introduction of several hundred cubic centimetres of gas.

The attempt to find any contraindication in the history is unsuccessful. Only one case had had a previous pleurisy with effusion, one case had had dry pleurisy on the treated side, and one patient bronchopneumonia nine months previous to the attempt at treatment. X-ray study is as little helpful, as will be seen in the next paragraph.

X-RAY STUDY OF 44 CASES

Roentgenographic study was made of 44 cases, 6 of these being cases in which attempts to induce pneumothorax were not successful. In all, 237 roentgenograms were studied, including, in most of the cases, one taken before treatment was instituted and others at varying time intervals. Special attention was given to the condition of the untreated lung before and after pneumothorax was induced, the presence of cavities, roentgenographic evidence of pleural adhesions before treatment and their occurrence after treatment, the effect on the contralateral lung, and an examination of the evidence for selective collapse described by Barlow.

In comparing the clinical classification of the 44 cases with the X-ray findings, it became apparent that if roentgenographic evidence were to be added to the classification, as recently suggested by the American Sanatorium Association, 13 of the patients classified as Moderately Advanced would have to be placed in the Far Advanced group.

Of the 44 cases, 35 showed parenchymatous infiltration, involving more of the lungs than an area to the second chondrosternal articulation on both sides or to the third chondrosternal articulation on one side. Six of the cases showed involvement somewhat less than this, but occupying more of the lung than that portion lying above the second chondrosternal junction on one side. In 2 of the cases such classification was impossible, on account of the fact that no plate was taken before collapse was produced.

The condition of the contralateral lung is shown in table 7.

Definite cavities were seen in 23 cases, while evidence of probable pleural adhesions (diaphragmatic adhesions, thickened pleura) was seen in 16. After the induction of pneumothorax definite adhesions were clearly visualized in 22 cases. In 8 cases more or less massive effusions

TABLE 7

No lesion seen	4
Peribronchial lesion only	11
Slight infiltration; small portion of one lobe	16
Marked infiltration; confined to one lobe	4
Infiltration involving 2 lobes	6
Infiltration with cavities	2

were seen, while in 4 plates traces of fluid were seen at the costophrenic angle, which disappeared on subsequent plates. A definite spread of lesion to the other lung, as evidenced by fresh parenchymatous infiltration, was seen in 10 patients, 4 of these showing no clinical evidence of such a spread; 2 patients developed severe dry pleurisy in the contralateral lung; and in 3 cases there was a slight increase in an already present lesion. It was interesting that the spread in 5 of the cases was almost identical, an interlobar pleurisy with parenchymatous infiltration occurring in the second and third interspaces in the right lung.

SELECTIVE COLLAPSE

It is stated by Barlow (2) that, when small amounts of gas are introduced into the pleural cavity, the gas tends to localize over the portion of the lung showing the greatest evidence of tuberculous activity. As a large proportion of our cases fall in the partial pneumothorax group, a careful examination of the plates was made to determine whether such localization could be demonstrated.

In 18 out of the 38 cases, the lesion being most apparent in the upper lobe, definite selection of the most diseased portion of the lung for first collapse was shown. That this was not altogether a matter of gravity was demonstrated by the fact that even when examined under the fluoroscope in a horizontal position the gas maintained the same location. In one case of lung abscess localized in the lower lobe, the gas introduced produced collapse over the involved area in the lower lobe, the unaffected upper lobe showing no collapse. In a recent case, the lesion being situated in the upper half of the lower lobe, the initial collapse took place over the apex, but on subsequent injections of gas the lower lobe maintained a complete collapse, the upper lobe showing only a slight area of pleural separation over the apex.

Of the 20 cases not showing definite selective action of collapse, 11 had widespread involvement of almost the entire lung, so that uniform collapse, such as occurred here, might well be classed as selective in action. In 2 of the cases examined a massive pleurisy with effusion was present, obscuring any selective action. In 4 no plate was made before collapse, so that the most involved area could not be determined. In only 2 of the cases did collapse occur against the rule of selective action. No definite explanation of these apparent exceptions could be deduced from study of the plates. However, in one of the two, while the first injection of gas localized over the lower lobe, the lesion being in the upper half, later injections brought about a collapse of the upper lobe, the lower apparently reëxpanding. The selective action of partial collapse described by Barlow would seem to be substantiated in the small series of plates studied.

Two patients proved of special interest from the standpoint of the curative action of pneumothorax. In one, collapse of the upper lobe had been maintained for about ten months. The patient then went away for a short vacation and the lung almost entirely reëxpanded. A plate made at this time showed very definite increase in the area and density of the lesion in the portion of the lung which had been collapsed. The patient had been doing well and showed no evidence of renewed activity. Collapse was reproduced without difficulty and is still being maintained eight months later. The patient is up and around but has failed to gain, still having considerable cough and expectoration and a general feeling of lassitude. In the other case reëxpansion occurred owing to the patient's temporary absence from the Sanatorium, and the plate made showed almost complete disappearance of the dense shadow in the

involved upper lobe. Treatment in this case had been kept up for about seven months. One other patient was of interest in the same respect. In his case pneumothorax treatment was kept up for over a year, and finally abandoned on account of the formation of dense pleural adhesions. Examination of recent plates shows some increase in fibrosis but relatively little change in the pulmonary shadows. These plates go to support the impression obtained from our experience with pneumothorax therapy that the collapse *per se* has little if any curative action. It merely places the patient in a more favorable condition to go on with the usual cure.

REVIEW OF RECENT LITERATURE

An attempt to tabulate the results given in a few recent publications, reporting end-results in pneumothorax, has proved impossible owing to the great differences in the methods of presentation of the various authors. Thus, Saugman (3) reports 310 cases, dividing them into two classes. Those that kept up the treatment comprised 71 per cent. Of these, 59.3 per cent died of tuberculosis, 28.0 per cent of other causes, 33.9 per cent are able to work and 3.2 per cent unable to work. Of the 29 per cent who abandoned treatment after a short time, 85.9 per cent are dead from tuberculosis and 2.2 per cent from other causes; while 19.9 per cent are able to work and 1.1 per cent unable to work.

Rickmann (4) reports 81 cases: 24 improved and 57 with immediate improvement or 66 per cent of those who had six or more months of treatment.

Dorn (5) reports two series, the first treated from 1911 to 1916, comprising 20 cases of which 18 are dead and 2 living. All of this series were of the far advanced type. The second series of 58 were treated from 1917 to 1920. Thirty-one of these are still alive and taking treatment; of these 19 are able to work. Of the 20 cases who have discontinued treatment 13 are able to work.

Gravesen (6) reports 60 cases: 6 dead, 7 with relative recovery (able to work), 16 with marked improvement, 17 improved, 1 no change, 11 worse or died, and 2 dead from influenza.

Harns (7) reports 193 cases between the years of 1912 and 1919. Ninety-two are dead, 53 still alive, 48 unknown, 7 clinically healed, 65 capable of work, and 33 still living and working.

Liebe (8) reports 104 cases; 34.6 per cent died, 10.9 per cent doing poorly, and 39.7 per cent doing favorably.

Deist (9) has 39 cases, with 27 deaths and 12 alive. Of these 8 may be considered healed. Of 44 cases since 1918, 12 are dead, 32 living, 23 materially improved.

Ringer (10), at the last meeting of the National Tuberculosis Association, reported 101 cases in his practice since 1912. Forty-one are dead, 5 dying, 25 living but unable to work, 4 able to work and 16 unknown; or, eliminating the latter group, died 48.2 per cent, dying 5.8 per cent, living 19.4 per cent, well 16.4 per cent. Stivelman (11) reported, in the discussion at the same meeting, 78 cases, with 57 per cent improved and 30 per cent discharged as arrested.

The difficulty of putting the results of pneumothorax treatment in statistical form is of course fully realized, as so many factors come into consideration that make a fair comparison of results impossible; the type of case selected for treatment, duration of treatment, age and possibly sex, all may have a profound influence on the ultimate results obtained. The somewhat discouraging facts of cold statistics as to ultimate results fail entirely to disclose the more encouraging side of the work; namely, the marked amelioration of symptoms, disappearance of cough and expectoration, disappearance of fever, gain in weight and general morale that so frequently result even in the purely palliative employment of the treatment when the improvement is but temporary.

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ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS

A STUDY OF 109 CASES

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Through the kindness of Dr. Joseph Walsh, under whose direction this study was made, we were permitted to examine the case records of the White Haven Sanatorium. One hundred and eighty patients have been treated there by artificial pneumothorax since 1912. We have examined the records of all these, and have collected for compilation the facts in 109, in 107 of which the procedure had been done more than five times. The diagnosis in all but one was tuberculosis of the lungs; in this one it was lung abscess.

In all of the earlier cases the injections of gas or air were given by Dr. Alexander Armstrong; of late years they have been given by a member of the resident staff under Dr. Armstrong's direction. The patients treated have been those of Drs. Lawrence F. Flick, Joseph Walsh, H. R. M. Landis, Henry M. Neale, Frank A. Craig, Charles J. Hatfield, Ward Brinton, A. J. Cohen, John W. Busch, Charles M. Montgomery, Alexander Armstrong, Isadore Kaufman, John B. Flick and Elmer H. Funk.

The indications for the induction of pneumothorax were hemorrhage, or persistent oozing which could not be controlled by simpler methods, failure to respond to routine treatment, and sometimes the idea of the lessening of toxicity by lowering temperature, decreasing expectoration or relieving cough, and in certain earlier cases to test the value of a method which was receiving commendation from other clinicians. Recourse was had to the method only after the patient had been carefully studied by one of the visiting physicians in his private practice, or after residence in the Sanatorium. The control of collapse was determined by repeated physical examinations, and later by the combined use of this method and the X-ray, the latter by both the fluoroscope and stereoscopic plates.

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AGE

Two patients were between the ages of 10 and 15 years; one was improved on discharge, the other was not. Seventeen patients were between 15 and 20; of these, 4 were improved, 11 unimproved and 2 died. Thirty patients were 20 to 25; 12 were improved, 11 unimproved and 7 died. In the group between 25 and 30 years there were 24 patients; of these 9 were improved, 11 unimproved and 4 died. Sixteen were between 30 and 35; of these 8 were improved, 4 unimproved and 4 died. Six were between 35 and 40; 4 were improved and 2 unimproved. In the group between 40 and 45 there were 8 patients; 4 improved and 4 died. Three patients were between 45 and 50; one was improved, one unimproved and one died. Of the two patients between 50 and 55, one was improved and one unimproved. One patient whose age was unknown was improved. (Table 1.)

TABLE 1

Age

	IMPROVED		UNIMPROVED		DIED		TOTAL	PER CENT IMPROVED	PER CENT UNIMPROVED	PER CENT DIED
	Unilateral	Bilateral	Unilateral	Bilateral	Unilateral	Bilateral				
10–15 years	0	1	0	1	0	0	2	50	50	
15–20 years	0	4	2	9	0	2	17	23.5	64.7	11.7
20–25 years	2	10	2	9	1	6	30	40	36.6	23.3
25–30 years	1	8	2	9	0	4	24	37.5	45.8	16.6
30–35 years	0	8	1	3	0	4	16	50	25	25
35–40 years	1	3	1	1	0	0	6	66.6	33.3	33.3
40–45 years	1	3	0	0	0	4	8	50		50
45–50 years	0	1	0	1	1	0	3	33.3	33.3	33.3
50–55 years	0	1	0	1	0	0	2	50	50	
Unknown	0	1	0	0	0	0	1	100		
Total.....	5	40	8	34	2	20	109			

DURATION

The duration previous to the time of admission as dated by the patient from the recognition of his first symptom, or as determined by the history, ranged from one month to more than three years. Twenty-three were under six months; of these, 4 were unilateral, and 19 were bilateral; 10 were discharged improved, 7 unimproved and 6 died. Twenty-one were between six months and one year; they were all bilateral; 10 were improved, 6 unimproved and 5 died. The duration of

illness in 20 was between twelve and eighteen months; of these, 4 were unilateral and 16 bilateral; 6 were improved, 10 unimproved and 4 died. In 7 the duration was from eighteen to twenty-four months; 1 was unilateral and 6 bilateral; 2 were improved, 3 unimproved and 2 died. Two to three years was the duration as determined in 15; all were bilateral; 6 were improved, 8 unimproved and 1 died. In eighteen the duration was more than three years; 5 were unilateral and 13 bilateral; 11 were improved, 6 unimproved and 1 died. In 5 patients the duration was not known. (Table 2.)

TABLE 2

Duration

	1–6 MONTHS	6–12 MONTHS	12–18 MONTHS	18–24 MONTHS	2–3 YEARS	3 YEARS	UNKNOWN
Improved	10	10	6	2	6	11	
Unimproved	7	6	10	3	8	6	2
Died	6	5	4	2	1	1	3
Bilateral	19	21	16	6	15	13	4
Unilateral	4		4	1		5	1
Total	23	21	20	7	15	18	5
Per cent	21.1	19.2	18.3	6.4	13.76	16.5	4.58
Per cent improved	43.46	47.61	30	28.57	40	61.1	
Per cent unimproved	30.43	28.55	50	42.8	53.3	33.3	
Per cent died	26.08	23.8	20	28.57	6.6	5.5	

INVOLVEMENT

The involvement, as determined by physical examination, was unilateral in 15 cases and bilateral in 94.

Of the 15 unilateral cases, 8 showed simple infiltration; and of these 4 were improved, 2 unimproved and 2 died. Seven had infiltration with cavitation, and of these but 1 was improved and the remaining 6 unimproved.

The 94 bilateral cases comprised 40 with infiltration and 54 with infiltration and cavitation. Twenty-two of the former were improved, 8 unimproved and 10 died. Of the group with the more marked anatomic changes, 18 were improved, 26 unimproved and 10 died.

Of the 48 cases with infiltration, only 26 or 54.1 per cent were improved, 10 or 20.8 per cent unimproved, and 12 or 25 per cent died.

The 61 cases with cavitation had improvement shown in but 19 or 31.1 per cent, while 32 or 52.4 per cent were unimproved, and 10 or 16.3 per cent died. (Table 3.)

TABLE 3

Involvement

		IMPROVED		UNIMPROVED		DIED	
Infiltration	Unilateral.....	4	26 (54.1%)	2	10 (20.8%)	2	12 (25%)
	Bilateral.....	22		8		10	
Infiltration and cavitation	Unilateral.....	1	19 (31.1%)	6	32 (52.4%)	0	10 (16.3%)
	Bilateral.....	18		26		10	

TUBERCLE BACILLI IN SPUTUM

The sputum was positive for tubercle bacilli in 100 cases; 5 were repeatedly negative; 2 patients had no expectoration; and in 2 there were no records. A negative sputum occurred in the abscess case; the other instances of its occurrence were in bilateral cases. Of the patients who did not expectorate one was a bilateral case and the other unilateral.

The patients with negative sputum were discharged as improved in 2 cases and unimproved in 2, and the case with the pulmonary abscess terminated fatally. (Table 4.)

TABLE 4

Tubercle bacilli in sputum

	PRESENT	ABSENT	NO EXPECTORATION	NO RECORD
Unilateral cases.....	13	1	1	
Bilateral cases.....	87	4	1	2
Total.....	100	5	2	2

IMPROVED	UNIMPROVED	DIED
Negative sputum		
2	2	1 (abscess)
Positive sputum		
43	40	21

WEIGHT LOSS BEFORE ADMISSION

The total weight loss before admission of 45 patients discharged as improved was 783 pounds, an average of 17.4 pounds per patient. Of those discharged as unimproved, 42 patients, the total weight loss was 894.1 pounds, an average of 21.2 pounds per patient. The total weight loss of the twenty-two patients who died in the Sanatorium was 687.7 pounds, an average of 31.2 pounds per patient.

In the unilateral cases 111 pounds were lost by 5 patients who were improved on discharge, an average of 22.2 pounds per patient. Of those who were unimproved, the minimum loss was 1.5 pounds and the maximum 24, the average being 13.3 pounds. The 2 patients of this group who died lost weight before admission; one, the patient with the pulmonary abscess, lost 40 pounds; the weight of the other was unknown.

TABLE 5

Weight loss before admission

	IMPROVED	UNIMPROVED	DIED
All cases	783	894.1	687.2
Average per patient	17.4	21.2	31.2
Unilateral (average loss)	22.2	13.3	40.0*
Bilateral (average loss)	17.2	20.9	30.7
Males (average loss)	17.4	18.6	30.5
Females (average loss)	16.1	19.1	30.3

* This was the weight loss of the patient with the pulmonary abscess. In the other patient with unilateral involvement the amount lost was unknown.

The bilateral patients who were discharged as improved lost 17.2 pounds per patient; the unimproved 20.9 pounds; and those who died in the Sanatorium lost 30.7 pounds as an average.

Considered as to sex, the male patients who improved lost 17.4 pounds per patient, the unimproved 18.6 pounds, and those who died 30.5 pounds per patient. For the female patients the average loss for those who were discharged as improved was 16.1 pounds, for the unimproved 19.1 pounds, and for those who died 30.3 pounds. (Table 5.)

LENGTH OF PRELIMINARY TREATMENT

By this we mean the length of the routine sanatorium treatment previous to the administration of pneumothorax.

Many of the patients had been seen by members of the visiting staff prior to their admissions and were sent directly to the Sanatorium for the express purpose of having the pneumothorax treatment. For this reason the period of preliminary observation was relatively brief. In 44, or 40.3 per cent, the period of observation was from one to thirty days. Fifteen, or 13.7 per cent, were observed from one to two months. In 14 or 12.5 per cent it was from two to three months. The preliminary study was from three to four months in 9 patients, or 8.25 per cent. Nine were studied from four to five months. Six patients, or 5.55 per cent, were in the group whose period of observation was from five to six months. Three patients fall into each of the next two groups;

TABLE 6

Length of preliminary treatment

PERIOD OF OBSERVATION	IMPROVED	UNIMPROVED	DIED	TOTAL	PER CENT IMPROVED	PER CENT UNIMPROVED	PER CENT DIED
1–30 days	21	14	9	44	47	31.8	20.4
1–2 months	5	5	5	15	33	33	33
2–3 months	7	5	2	14	50	35.7	14.2
3–4 months	3	4	2	9	33.3	44.4	22.2
4–5 months	3	5	1	9	33.3	55.5	11.1
5–6 months	1	4	1	6	16.6	66.6	16.6
6–7 months	1	2		3	33.3	66.6	
7–8 months	2	1		3	66.6	33.3	
8–9 months	1			1	100		
9–10 months	1	1		2	50	50	
10–11 months			1	1			100
12–18 months		1		1		100	
24–36 months			1	1			100

they each represent 3.75 per cent of the total. One patient was studied from eight to nine months, 2 from nine to ten, and one from eleven to twelve. One was observed from twelve to eighteen months; and one was in the Sanatorium for more than two years before the treatment was started. (Table 6.)

WEIGHT CHANGE UNDER PRELIMINARY TREATMENT

Forty-seven patients, or 43.1 per cent of the total, showed a gain in weight under the preliminary treatment; of these, 25 or 53.1 per cent were discharged as improved, 16 or 34 per cent unimproved, and 6 or 12.7 per cent died.

The total gain of the 25 who were discharged as improved was 199 pounds in 356 weeks, a gain of 7.56 pounds per patient. Those who were unimproved gained 93.5 pounds in 306 weeks, an average of 5.8 pounds per patient. The six who died gained a total of 29.5 pounds in 208 weeks, or 4.9 pounds per patient.

The average weekly gain was 0.55 pound for those who were improved, 0.305 pound for the unimproved and 0.139 for those who died.

The weights of 35, or 32.1 per cent of the patients, remained stationary; of these, 14 or 40 per cent were improved, 13 or 37.1 per cent unimproved, and 8 or 22.8 per cent died.

In 27 patients, who represent 24.7 per cent of the total, there was a loss of weight under preliminary treatment. Of these, 6 or 22.2 per

TABLE 7

Weight change under preliminary treatment

WEIGHT CHANGE	NUMBER OF PATIENT	PER CENT OF PATIENTS	NUMBER OF WEEKS	IMPROVED	UNIMPROVED	DIED	PER CENT IMPROVED	PER CENT UNIMPROVED	PER CENT DIED
Gained	47	43.1	870	25	16	6	53.1	34	12.7
Stationary	35	32.1	147	14	13	8	40	37.1	22
Lost	27	24.7	246	6	14	7	22.2	51.7	25.9

Average gain or loss per week

WEIGHT CHANGE	IMPROVED	UNIMPROVED	DIED
Gained	0.55	0.305	0.139
Lost	0.271	0.562	0.31

cent improved, 14 or 51.7 per cent unimproved, and 7 or 25.9 per cent died. The 6 patients who improved lost 14.5 pounds in 53 weeks, a loss of 0.27 pounds per week; the 14 unimproved lost 87 pounds in 153 weeks, or 0.562 pounds per week; and the 7 who died lost 12.5 pounds in 40 weeks, or 0.31 pounds per week. (Table 7.)

DURATION OF PNEUMOTHORAX TREATMENT

In 12 cases the treatment was suspended within thirty days; one unilateral case was improved; the remainder were bilateral, of which 4 were improved, 2 unimproved, and 5 died in the Sanatorium. In the second group 32 patients were treated for one to two months; 4 were unilateral, of which 1 was improved, 1 unimproved and 2 died; of the 28 bilateral, 8 were improved, 11 unimproved and 9 died. Seven-

teen patients were treated from two to three months; 3 unilateral cases were unimproved; of the 14 bilateral, 4 were improved, 7 unimproved and 3 died. The treatment was between three and four months in 13; three were unilateral, of which 2 were improved and 1 unimproved; 10 were bilateral, and of these 5 improved, 3 unimproved and 2 died. In 5 the treatment was from four to five months; the only unilateral case was discharged as improved; of the 4 bilateral, 3 improved and 1 did not. Treatment was between five and six months in 10 cases; the one unilateral case was unimproved; of the 9 bilateral, 7 were improved and 2 unimproved. Of 7 patients in the six to seven month group, one, a unilateral case, was unimproved; and of the bi-

TABLE 8

Length of pneumothorax treatment

LENGTH	BILATERAL				UNILATERAL				TOTAL	PER CENT
	Improved	Unimproved	Died	Total	Improved	Unimproved	Died	Total		
1–30 days	4	2	5	11	1			1	12	11
1–2 months	8	11	9	28	1	1	2	4	32	29.3
2–3 months	4	7	3	14		3		3	17	15.5
3–4 months	5	3	2	10	2	1		3	13	11.9
4–5 months	3	1		4	1			1	5	4.5
5–6 months	7	2		9		1		1	10	9.1
6–7 months	3	3		6		1		1	7	6.4
7–8 months	1	1		2					2	1.8
9–10 months	1			1		1		1	2	1.8
10–11 months	1	1	1	3					3	2.7
11–12 months	1	1		2					2	1.8
12–13 months		2		2					2	1.8
13–14 months	1			1					1	0.91
16–17 months	1			1					1	0.91

lateral, 3 improved and 3 did not. Two bilateral cases, one improved and one unimproved, were treated from seven to eight months. One bilateral case treated from nine to ten months was improved and one bilateral case was unimproved. Three patients, all with bilateral involvement, were treated from ten to eleven months; one was improved, one unimproved, and one died. The treatment was from eleven to twelve months in 2 bilateral cases; one improved and the other did not. Two bilateral cases treated between twelve and thirteen months were unimproved. One bilateral case treated from thirteen to fourteen months, and one treated from sixteen to seventeen months, were discharged as improved. (Table 8.)

NUMBER OF INJECTIONS

The number of injections ranged from 2 to 50. Two patients received less than 5; one was improved and one died. Forty received between 5 and 10; of these, 10 were improved, 16 unimproved and 14 died. Twenty-three received from 10 to 15; of these, 9 improved, 10 unimproved and 4 died. Injections were given between 15 and 20 times to 19 patients; 10 were improved, 7 unimproved and 2 died. In 8 the number was between 20 and 25; 6 improved and 2 did not. Eleven were given from 25 to 30 injections; 6 were improved, 4 unimproved and 1 died. Two received between 30 and 35 injections; one was improved and one unimproved. Two, both of whom were improved, received 36 injections. Two who were unimproved received 40. (Table 9.)

TABLE 9

Number of injections

INJECTIONS	NUMBER OF PATIENTS	IMPROVED	UNIMPROVED	DIED	PER CENT IMPROVED	PER CENT UNIMPROVED	PER CENT DIED
Less than 5	2	1		1	50		50
5–10	40	10	16	14	25	40	35
10–15	23	9	10	4	39.1	43.4	17.2
15–20	19	10	7	2	52.6	36.8	10.5
20–25	8	6	2		75	25	
25–30	11	6	4	1	54.5	36.3	9.0
More than 30	6	3	3		50	50	

WEIGHT CHANGE UNDER PNEUMOTHORAX

Of the 45 patients, who were discharged as improved, 30 or 66.6 per cent gained weight while under pneumothorax, 8 or 17.7 per cent remained stationary, and 7 or 15.5 per cent lost. The 30 who showed a weight increase gained 328 pounds in 461 weeks, or 0.71 pounds per week; the 7 whose weights decreased lost 53.5 pounds in 158 weeks, or 0.338 pounds per week.

Forty-two patients were discharged as unimproved, 25 or 59.5 per cent gained in weight under pneumothorax, 1 or 2.3 per cent remained stationary, and 16 or 38 per cent lost. The 25 who gained, gained 605 pounds in 289 weeks, an average of 0.209 pounds per week; of the 16 who lost, in 5 the amount was unknown, and the 11 in whom the amount was known lost 164.5 pounds in 286 weeks, an average of 0.57 pounds per week.

Of the 22 patients who died in the Sanatorium, 3 or 13.6 per cent gained 11.4 pounds in fourteen weeks, an average of 0.82 pounds per week. In 19, or 86.3 per cent, who failed to gain, the amount of the loss was known in 5 cases to be 61 pounds in 72 weeks, an average of 0.84 pounds; in 14 the amount of loss was unknown. (Table 10.)

TABLE 10

Weight change under pneumothorax

WEIGHT CHANGE	IMPROVED			UNIMPROVED			DIED			
	Number of patients	Number of weeks	Average per week	Number of patients	Number of weeks	Average per week	Number of patients	Number of weeks	Average per week	Per cent all patients
Gain	30	461	0.71	25	289	0.209	3	1.41	0.82	53.2
Stationary	8			1						8.2
Lost	7	158	0.33	16		0.57†	19		0.84*	38.5

		PER CENT
Gained	Improved	51.7
	Unimproved	43.1
	Died	5.1
Stationary	Improved	88.8
	Unimproved	11.1
	Died	
Lost	Improved	45.2
	Unimproved	38.0
	Died	16.1

* Based on known loss in 5 patients; in others loss unknown.

† Based on known loss in 11 patients; in others loss unknown.

LENGTH OF ROUTINE TREATMENT AFTER PNEUMOTHORAX

Twelve patients left the Sanatorium within twenty-four hours of the last injection; of these, 4 were discharged as improved, 6 unimproved, and 2 died within that time. Forty-seven were discharged within thirty days of the discontinuance of the treatment; 20 improved, 19 unimproved and 8 had died. Thirteen remained from two to three months; 4 were discharged improved, 5 unimproved and 4 died. Six left the Sanatorium between the third and fourth months, 5 as improved and 1 unimproved. Five were discharged between the fourth and

fifth months, 1 as improved and 4 unimproved. Two patients, one of whom died and the other improved, were in the fifth to the sixth month group. Three were discharged between the sixth and seventh months; 2 improved and 1 died. One improved patient was discharged in the seventh month; and 3, of whom 2 were improved and 1 unimproved, in the eighth month. Three, of whom one was improved, one unimproved and one died, were in the ninth month. One in the twelfth month was unimproved; one died in the fourteenth month; and one was unimproved on discharge after thirty-three months. (Table 11.)

TABLE 11

Length of routine treatment after pneumothorax

DURATION	NUMBER OF PATIENTS	IMPROVED	UNIMPROVED	DIED	PER CENT IMPROVED	PER CENT UNIMPROVED	PER CENT DIED
Less than 1 day	12	4	6	2	33.3	50	16.6
1–30 days	47	20	19	8	42.5	40.4	16.6
1–2 months	11	5	2	4	45.4	18	36.3
2–3 months	13	4	5	4	30	39	30
3–4 months	6	5	1		83.3	16.6	
4–5 months	5	1	4		20	80	
5–6 months	2		1	1		50	50
6–7 months	3	2		1	66		33
7–8 months	1	1					
8–9 months	3	2	1		66	33	
9–10 months	3	1	1	1	33	33	33
10–11 months							
12–13 months	1		1				
14–15 months	1			1			
33 months	1		1				

WEIGHT CHANGE THE RESULT OF ROUTINE TREATMENT SUBSEQUENT TO PNEUMOTHORAX

Fifty-six patients were discharged whose weights were unknown; of these 18 were improved, 21 unimproved, and 17 died in the Sanatorium.

The discharge weights of the other 53 patients were known. Twenty-seven were improved; of these, 24 showed a gain in weight from the last injection until discharge; they gained 151 pounds in 285 weeks, an average of 0.53 pounds per week. Three who were discharged improved lost weight during this second routine treatment; the total loss for this group was 2.6 pounds in 19 weeks, or 0.13 pounds per week.

Twenty-one patients whose weights were known showed no improvement on discharge; of these, 4 had gained, 4 had remained stationary and 13 had lost. The 4 whose weights increased gained 9.5 pounds in 176 weeks, or 0.053 pounds per week. The weights of the 4 who remained stationary were for a total of 86 weeks. The total loss of the 13 patients who lost was 92.5 pounds in 149 weeks, an average loss of 0.63 pounds per week.

Five patients whose weights were known at death lost 12.3 pounds in 23.6 weeks, an average loss of 0.53 pounds weekly. (Table 12.)

TABLE 12

Weight change, the result of routine treatment subsequent to pneumothorax

PATIENT AT DISCHARGE	DISCHARGE WEIGHT UNKNOWN	GAINED	STATIONARY	LOST
Improved	18	24		3
Unimproved	21	4	4	13
Died in sanatorium	17			5
Totals	56	28	4	21

WEIGHT CHANGE	IMPROVED			UNIMPROVED			DIED		
	Number of patients	Number of weeks	Average per week	Number of patients	Number of weeks	Average per week	Number of patients	Number of weeks	Average per week
Gained	24	285	0.53	4	176	0.05			
Stationary				4	86				
Lost	3	19	0.13	13	149	0.63	5	118	0.53

SUMMARY

Of the 109 patients whose case records were studied, 45 improved, 42 were unimproved, and 22 died in the Sanatorium. We have attempted to work out the factors which determined the end-result.

Because in the great majority of cases of tuberculosis of the lungs the weight changes may be considered as fair criteria of prognosis and progress, we have based our conclusions on the changes in weight that took place during different stages of the patient's treatment.

Age: Discarding the first age group, which has but 2 patients, and considering the second to the seventh, which represent 17, 30, 24, 16, 6 and 8 patients respectively, we find that the percentage of improve-

ment increases with the age. If one considers that 15 of the 16 patients in the 30 to 35 years group have bilateral involvement, he finds that this particular group shows the greatest improvement.

Duration: The patients in whom the duration was from one to two years showed the least response to treatment. Patients whose disease age fell into either one of the two groups before or behind it show better results. Comparison of results in those, in whom the disease was known to have existed less than six months, and those who were in the second six months' period of its recognition, shows practically the same percentage of improvements, unimprovements and deaths.

Involvement: While it is easily understood that the case with unilateral involvement is the ideal one for pneumothorax, the usefulness of the method would be restricted to very narrow limits if it were reserved for this type of case only. In sanatorium practice at least, the greater number of patients have bilateral involvement, whether this is because the unilateral case, which is always the earlier, is cared for at home with good result, or because the disease is not recognized until it becomes massive and the patient is then sent to the sanatorium, we are not prepared to say. We do know that if the use of pneumothorax were limited only to those unilateral cases that did not do well under the ordinary regimen of rest, good food and fresh air it would have a very narrow field. At the White Haven Sanatorium it has been used in all varieties of cases, from those with simple infiltration of one lung to those with marked structural changes in both lungs.

In this series of cases the less extensive the involvement the greater has been the percentage of improvement, and, with an increase in the size of the lesion and greater anatomic changes, this percentage has declined. This is not at variance with the results one would expect, nor is it to be singled out in condemnation of pneumothorax; for it is true that any given treatment of tuberculosis will produce results varying in brilliance inversely with the extent of the involvement.

Tubercle bacilli in sputum: We are unable to draw any conclusions as to the influence the presence or absence of the tubercle bacilli in the sputum has on the prognosis. We are certain that their presence is not a contraindication to the treatment.

Weight loss before admission: A consideration of the cases presented from the point of weight loss on admission shows that the best results were obtained in those cases with the least loss, a factor which is recognized as influencing the prognosis in tuberculosis treated by any method. The wide variation in the loss of weight in those who were discharged

as improved and those who died is of interest. With the exception of the unimproved unilateral cases the other groups, studied in regard to both sex and involvement, confirm the statement that the percentage of improvement at discharge varies inversely with the preadmission loss of weight in any group of cases.

Length of preliminary treatment: This has had no demonstrable influence on the condition of the patients at discharge.

Weight change under preliminary treatment: The response to preliminary treatment, as indicated by weight increase, may be regarded as a fair index of the prognosis that is to be expected under pneumothorax. Not all patients who gained during this period were discharged as improved; but more were discharged improved from this group than were similarly discharged from the group that had lost during this preliminary period.

When the amount gained or lost is considered, we find that the patients who were improved were those who had gained the most or lost the least while in this stage of the treatment.

Length of pneumothorax treatment: In the one to thirty-day group the highest death rate is found; the percentage of improvement (41.6) was about the same as that obtained in the final results (41.27). Until the third month was reached the percentage of improvement is less than the discharge percentage; but from this period on, with the exception of the tenth month, it was always higher. All the deaths but one occurred within four months of the beginning of treatment; one death occurred between the tenth and eleventh months. The percentage of deaths is highest in the first group and gradually falls.

From this it may be concluded that, if the patient responds early in the course of his pneumothorax treatment, his chances of being discharged improved are increased. And with this early favorable response a continuation of the treatment may prove beneficial. The high death rate in the first sixty days of treatment suggests that the procedure may shorten life; for it is hardly possible that 20 per cent of the patients were of such advanced disease that they would have succumbed within four months had they been treated along routine lines.

Number of injections: It was not until after fifteen injections that the percentage of improvement for any group was equal to the percentage of improvement in the final results. The death rate was higher in the cases that were given less than ten injections than in those who received more. Unimprovement on discharge varied less in its percentage than did the other two discharge groups. These statements seem

to bear out our contention that the procedure may hasten a fatal termination; but that prolongation in the patients who survive is not so injurious and may be of benefit.

Weight change under pneumothorax: A comparison of this table with that of the weight under preliminary treatment shows that those patients whose weights remained stationary under the preliminary treatment were the ones most affected by pneumothorax. Of course, many of our patients were put on pneumothorax immediately after admission, and they were listed as stationary in weight. This accounts for the large number who fell under this classification in the first weight table.

The average gain per week was higher for those who improved by the pneumothorax than for those who were improved under the preliminary treatment. The average loss was also greater under this treatment than it was under routine. We infer from this that the procedure hastens the process; the case that is to improve gains that much more rapidly; the one not destined to improve arrives at a fatal termination in his illness earlier than he otherwise would have.

Length of routine treatment after pneumothorax: This bears no relation to the condition on discharge that we have been able to determine.

Weight change the result of routine treatment subsequent to pneumothorax: Of the 50 cases in which the change was known, those who had gained the most under this second routine treatment were those who were discharged as improved; and the patients who were discharged unimproved were those who had gained the least or lost the most, a condition similar to the weight change when the patients were first treated. The average gain was again less than it was under pneumothorax, and the losses averaged less than they had when the patients were under active pneumothorax treatment.

Deaths: Of the 22 patients who died in the Sanatorium five were examined postmortem. The findings in these cases are used by Walsh in his study on the clinical pathology of tuberculosis (AMERICAN REVIEW OF TUBERCULOSIS, 1923, vi, no. 11).

It is our intention to investigate the ultimate outcome of the patients who were discharged as improved. We hope to compare the results obtained by pneumothorax treatment with those from ordinary methods by studying an equal number of case histories of patients who were of the same age, sex, involvement, duration, and preadmission loss of weight as those reported in this paper, but who were treated by the usual sanatorium methods.

MEDIASTINAL SHIFTING IN ARTIFICIAL PNEUMOTHORAX

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Mediastinal shifting has been frequently reported and usually as occurring in patients under thirty years of age. Stivelman (1) and Barjon (2) comment on the comparative rarity of these mediastinal movements in pneumothorax cases. Rist (3), on the other hand, states that outside of the permanent displacement of the mediastinum by excess pressure of gas, there exists in a great number of pneumothorax cases periodic displacement of the mediastinum synchronous with the respiratory movement. This was first pointed out by Holzknecht (3) of Vienna in a case of unilateral bronchial stenosis. M. A. Beclere (3) has also shown this in connection with pleural adhesions. He thinks that this mediastinal displacement is almost constantly observed.

REPORT OF CASE

The patient is a priest of thirty-one. His family and early personal history were unimportant. There was an indefinite history of pulmonary tuberculosis for about six years. Four years ago, following an attack diagnosed as pneumonia, he developed frank pulmonary tuberculosis with tuberculous laryngitis. While he has been in a general hospital during the past three years, he has not been under medical supervision during this period.

When first seen on December 21, 1922, his principal complaint was that he tired very easily and had considerable cough and sputum. Examination at this time disclosed extensive old fibrosis in the right lung. The upper lobe of the left showed extensive infiltration, with cavitation above the third rib. Râles were heard throughout this area. Fluoroscopic examination showed marked increased density in the left upper lobe to the extreme apex. On the right was increased density with increased linear markings, interpreted as mostly fibrosis. No cavities were noted on the left on fluoroscopic examination, but there was adequate clinical evidence of the existence of multiple small cavities in this area.

The patient was referred for artificial pneumothorax. His condition had been stationary for at least two years with very little hope of improvement under existing conditions. He was advised that the evident adhesions in the

left apex might entirely prevent an adequate pneumothorax, but that an attempt was justifiable. The first pneumothorax was induced on December 27, 1922. A partial collapse of the lung was immediate. By January 9, 1923, approximately one-half of the lung was collapsed. On this date, a negative pressure still existing, there was some displacement of the heart to the right. By January 29, 1923, following the pneumothorax, which produced a collapse of about two-thirds of the lung, there was noted a clear area appearing to the right of the central shadow. This area was larger when viewed from the back, and seemed to disappear entirely on deep inspiration, reappearing on expiration and increasing in size on deep expiration. It was further noted that there was a fine basal adhesion to the diaphragm and that the left border of the collapsed lung occupied much the same position after the pneumothorax as before. On percussion there was very definite tympany in the second right interspace, which increased on expiration and disappeared on inspiration. In this region the inspiratory sound after cough had an amphoric quality. The whispered voice was better transmitted at the second left interspace than on the right. Observations at later dates have resulted in similar physical findings. From this it seemed that the additional air introduced at this time, which was 725 cc., distributed itself along the median border of the lung and was producing a mediastinal shifting. The pressures noted before the introduction of air on this date were -5, -3 and afterward $+0.5$, -0.5, which is practically a neutral pressure.

As a further check on the fluoroscopic findings, Doctor W. W. Wasson made the roentgen pictures which accompany this article. These show clearly a bow-shaped pocket extending from the first to the third intercostal space on the right side anteriorly, and from the fourth to the eighth vertebral spine posteriorly. The lateral view seems to indicate that the major portion of this lies posterior to the heart, although fluoroscopically there is evidence of air in the anterior mediastinum.

The patient did not note any serious discomfort at this or any other time. There has been some dyspnea on exertion with increased pulse-rate. With rest this immediately disappeared.

The general condition of the patient is improved. He has gained five pounds in the last five weeks with a total absence of symptoms, even the asthenia. From two ounces daily the sputum has now reduced to less than one dram.

With the appearance of this shifting, the patient was placed at absolute rest for several days. There were no untoward results. He was observed frequently during the succeeding weeks and this area was noted to be gradually disappearing.

The latest pneumothorax was performed April 4, 1923. This time the pressures before the insufflation were -17, -15. At no time prior had so

great a negative pressure been noted. After 1000 cc. of air were introduced the pressures were −3, −0.5.

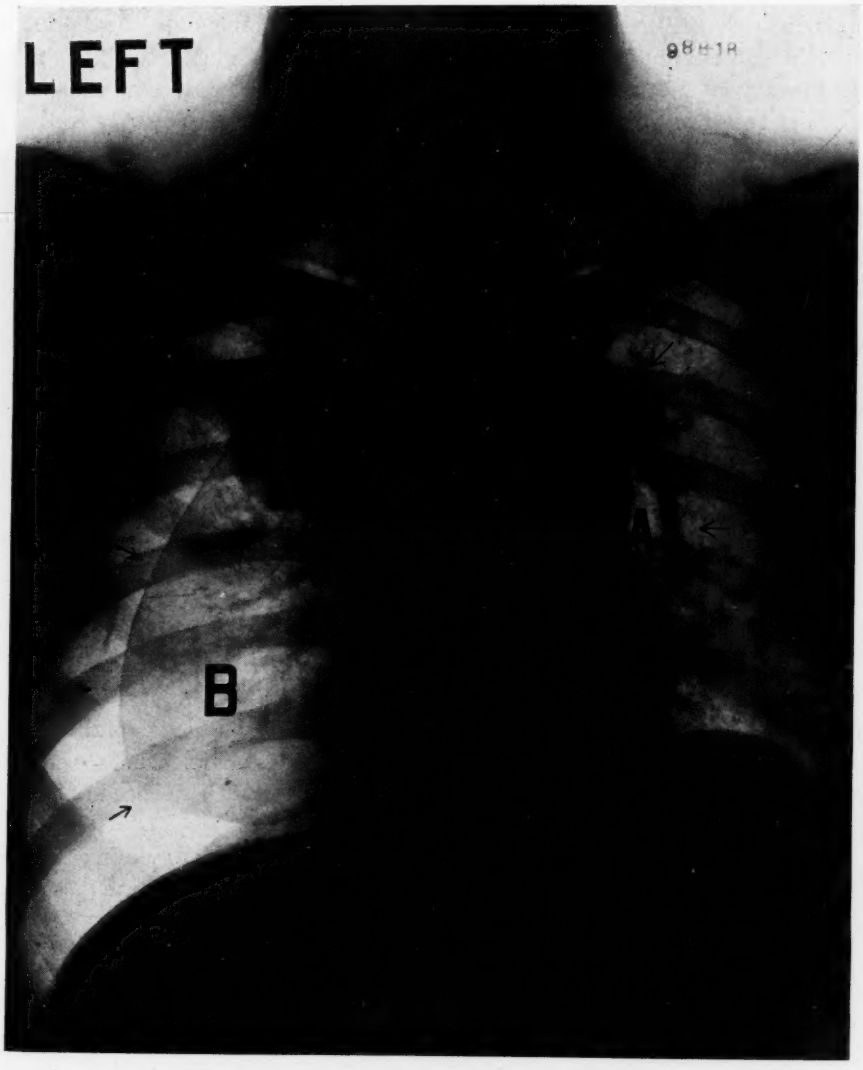

FIG. 1. TAKEN DURING DEEP EXPIRATION
(A) Area of mediastinal shifting. (B) Collapsed lung

Fluroscopic examination just before this procedure failed to show the displacement previously noted. After the introduction of 1000 cc. of air the displacement reappeared, but to a smaller extent than formerly. A further

point of interest is that there was not observed the constancy of pressure, "which does not increase with a continuation of the insufflation," which has been noted by Bernard (4) and others as a sign of mediastinal shifting.

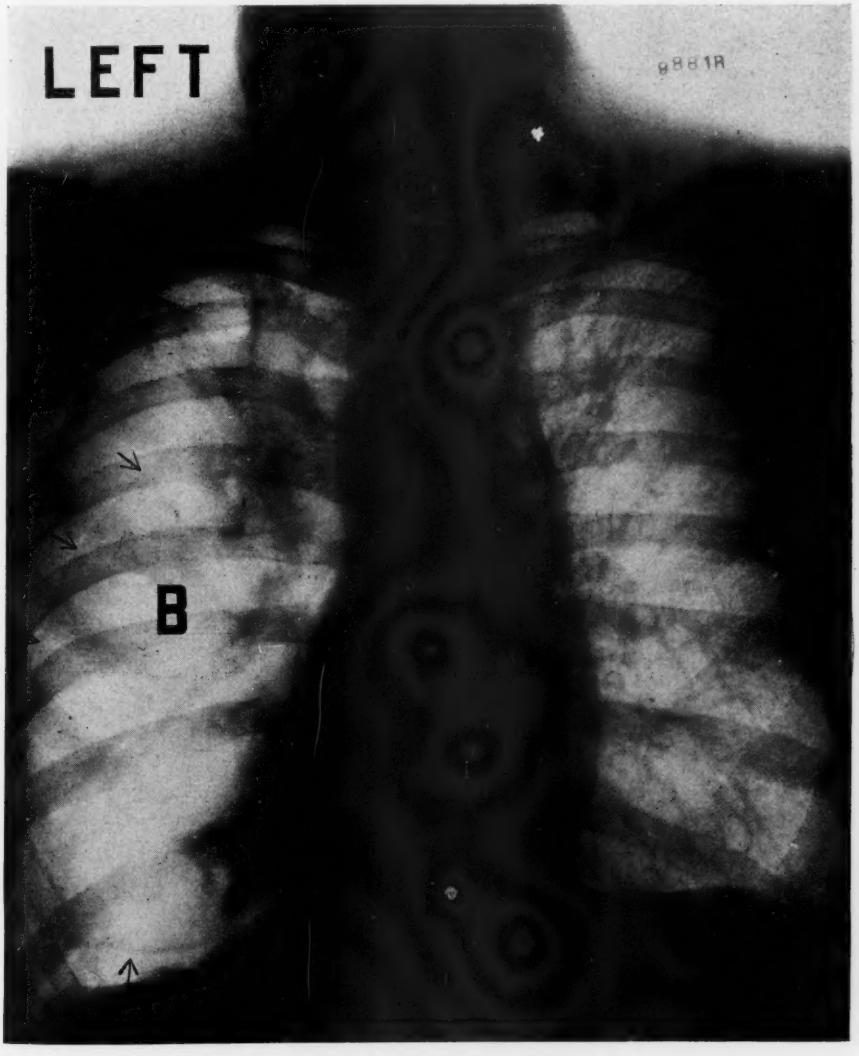

FIG. 2. TAKEN DURING DEEP INSPIRATION
(B) Collapsed lung shifted to left

While the case here reported is one of extreme shifting, the writer is under the impression that minor degrees of mediastinal shifting

are comparatively frequent in artificial pneumothorax. Most authors agree that it is very rare after thirty. Furthermore, it has been generally accepted that this usually occurs only with the higher pressures,

FIG. 3. IN ROTATED POSITION

sometimes following the breaking of an adhesion, which allows all of the structures to be pushed toward the opposite side. Bray (5) recently called attention to this phenomenon as one of the mechanisms

of compensation in pulmonary tuberculosis. Stivelman (1) describes at some length an inspiratory displacement of the mediastinum toward the pneumothorax side, terming it a "pendular movement of the mediastinum." A similar phenomenon first noted by Kienböck (6), commonly known as the "paradoxical movement of the diaphragm," occurs in certain pneumothorax cases, and is clinically recognized by a movement of the diaphragm in a direction reverse to that of normal, namely, the half of the diaphragm lying under the pneumothorax ascends on inspiration and descends on expiration. This, according to Sauerbruch (7), quoting Wellman, "is favorably influenced in that, as a result of the shifting of the mediastinum, the diaphragm is flattened and is hindered in its contraction. On inspiration through the return of the mediastinum it is more easily sucked up than under normal conditions." The idea which has been advanced frequently in the literature that this diaphragm phenomenon is caused by a paralysis of the affected side was experimentally investigated by Wellman (8) who, employing a galvanometer, demonstrated a definite muscular contraction occurring in the involved half. Barjon (2), discussing *mouvements de balance* offers, as one of the indispensable conditions for the production of the "paradoxical movement of the diaphragm," the *maintenance of a moderate positive pressure on the pneumothorax side.* Bittorf (9) has shown that, if a normal individual, while undergoing fluoroscopic examination, attempts deep inspiration with the nose and mouth closed, there will be seen a "double-sided paradoxical movement of the diaphragm;" because under such conditions there is an increased negative pressure in the thorax and because the inspiratory muscles of the thorax are stronger than those of the diaphragm, the latter is pulled up to descend again with expiration. He states further "the same diaphragmatic movement can occasionally be seen in artificial pneumothorax, *if there be a negative pressure.*" Stivelman (1), quoting Barjon (2), on the conditions causing the "paradoxical diaphragm," states that "the intrapleural pressure must be equal to or slightly greater than atmospheric pressure. It must be just enough to prevent air from entering the collapsed lung during inspiration, but not high enough to force and keep the diaphragm down;" and he further points out that this is equally applicable to the conditions causing the "pendular movement of the mediastinum." The same thoracic aspiration theory which has been advanced as an explanation of the "paradoxical movement of the diaphragm" may explain this movement; namely,

that on the side of the pneumothorax the absence of air penetration into the lung creates a negative pressure with resultant shifting, but Maingot, Rist and Bernard (4) hold that this occurs more frequently with positive pressures and Barjon (2) points out that it is more frequently observed where there is a feeble positive pressure (+4, +6) and that it diminishes appreciably with a stronger positive pressure (+12, +15). This may suggest that in the case here reported a higher pressure might cause a disappearance of this phenomenon, but conservatism calls for an avoidance of any higher pressures which might cause further displacement. If it is true that this phenomenon is observable only with low positive, or even negative pressures, there appears to be added reason for frequent fluoroscopic observations at each change in pressure, in order that any tendency to mediastinal displacement may be noted. It is thus seen that there is not a uniformity of opinion as to the conditions causing this phenomenon.

While rupture of a mediastinal hernia is possible it is certainly extremely rare. Jones (10) reports a case of rupture of the mediastinum in the course of performing an artificial pneumothorax, with air passing through the two pleural surfaces into the opposite lung. He states that he is unable to find reference in the literature to a similar case.

Weiss (11) in 1912 reported such a pneumothorax patient, who, following bodily strain, became suddenly dyspneic. Examination showed about half of the good lung compressed. Removal of air from the side originally compressed led to healing. The writer had one case of mediastinal rupture with subcutaneous emphysema of both sides of the neck. This was temporarily associated with pain in the neck and difficulty in speaking and swallowing. The recovery was complete in about three days and uneventful. This seemed to occur in the lower mediastinum following a pressure of +2, +4 and occurred during the operation. This was a bed patient who had not been subjected to frequent fluoroscopic examinations.

Nitsch (12) in 1911 described two "weak points" in the mediastinum, where rupture or shifting may occur under certain conditions. The first or upper point lies anteriorly, at the site of the atrophied thymus, and extends from about the first to the third rib under the sternum. In the adult the resistance offered in this position may be very slight, and depends upon the condition of the thymus rest. The second, or lower weak spot, is found posteriorly and below, lying between the aorta and oesophagus, and from the level of the fifth to the twelfth

vertebral spine. Sauerbruch (7) states that "in the region of the lower posterior weak place (of the mediastinum) excessive swelling only seldom occurs, for the conditions here are not favorable. The mediastinal surface presses here directly against the mass of the good lung and finds a certain resistance. Swellings in this region do not usually cause considerable pain or much influence on the therapeutic result, they represent more an accidental finding." Nitsch (12) has explained why when a bulging occurs in this position, it is usually from right to left, an observation made also by Sauerbruch (7). The right pleura in this position usually occupies the midline, because the aorta and the oesophagus lie somewhat to the right. Schematically, he shows that with right-sided pressure the pleura will be pushed directly between these structures, exerting a wedge-like effect, while when the pressure comes from the left these structures are pressed together in such a way that the oesophagus overlaps the edge of the aorta as one tile overlaps another, thus effectively closing the left half of the thorax.

> Slight grades of such inflation often occur without pain, yet there often is a feeling of pressure upon the affected side, with oppression in the neck, the feeling as though something was torn inside, also an irritative cough and above all increased dyspnea. If it is also demonstrated by anterior fluoroscopy that the hernia has a depth of only a few centimetres, doubtless the breathing surface of the good lung will be appreciably reduced and its respiratory efficiency limited. The damage results often in the appearance of fresh tuberculous processes which are recognizable in the region of the hernia. (Quoted from Sauerbruch (7).)

The air pocket in the case here presented clearly lies between the first and third intercostal spaces anteriorly and between the fourth and eighth vertebral spines posteriorly. This anteriorly is in relation to the "upper weak spot" but the position as seen posteriorly is somewhat confusing. The lateral view and fluoroscopic manipulation seem to indicate that this lies mainly posterior to the heart. That it is not entirely posterior is shown by fluoroscopic examination and also by the marked tympany over the second and third right intercostal spaces, which disappears on deep inspiration. The weight of evidence is in favor of a hernia or shifting at the upper spot of Nitsch.

This case is submitted to emphasize (1) the necessity of frequent X-ray control of every case undergoing artificial pneumothorax, (2) to point out that unless the patient is a complete bed patient a fluoroscopic

observation should be made before and after each injection of air (in this case, if this had not been done, a higher positive pressure might have been established with very serious results), and (3) that physical signs, while of value, are not sufficiently dependable in the presence of pneumothorax.

December 24, 1923: Since this report was submitted for publication the collapse has been maintained. Pressures before and after the insufflation have remained practically as noted above. The amount of collapse has quite appreciably increased, but the "air pocket" noted in this report gradually decreased until observations made during November and December have failed to disclose any evidence of its presence.

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INTRAPERITONEAL OXYGEN INFLATIONS IN THE TREATMENT OF ASCITIC TUBERCULOUS PERITONITIS

WITH REPORT OF A CASE

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It was about a year ago that Arthur Stein reported what presumably was the first case of tuberculous exudative peritonitis treated by repeated peritoneal oxygen inflations. To date no further cases so treated have been reported in the literature. It may be that the method is considered too simple and easy of use to require further comment or, what is more likely, that the method has escaped the attention it deserves from a profession much preoccupied with apparently more important problems. It is with the hope of again calling attention to this valuable procedure that the following case is reported.

CASE REPORTS

J. R., white, male, age 29, admitted to Muirdale Sanatorium January 18, 1922.

Family History: No family history of tuberculosis.

Past History: Unimportant.

Present Illness: Began November 29, 1921, with pleurisy with effusion in left side. Was tapped and approximately three pints of straw-colored fluid withdrawn previous to admission.

On admission, patient had no cough, slight expectoration, had never had hemoptysis, no dyspnea, some pain in front of chest over left upper lobe on deep breathing. The appetite was good, bowels regular, no history of indigestion. No symptoms relating to urinary tract or central nervous system. Slight general malaise, no aphonia, has had slight night sweats. Temperature 37°C. Pulse 92 to 110. Says sputum was negative before admission. Patient progressed nicely since admission, gaining 7.5 kilos. On October 2, 1922, was transferred to St. Mary's Hospital, Milwaukee, to have tonsils removed because his family physician had previously so advised. Returned to Muirdale after three days at St. Mary's, to continue treatment for pulmonary condition. About October 26, 1922, patient began to notice his abdomen becoming

larger. This enlargement continued despite catharsis and enemas, causing dyspnea from pressure on thoracic viscera. He complained bitterly of this distention; and was nauseated and unable to retain most foods, including liquids at times. Pneumoperitoneal oxygen inflation was advised for diagnosis and treatment and he was transferred to the County Hospital where this procedure was carried out.

Physical Examination: Weight 56.6 kg., did not appear very ill, except for dyspnea caused by abdominal distention. Temperature 100.5° to 101° by mouth for one week prior to present examination. Chest normal in shape, slight diminution of expansion on left side especially at base. Diaphragmatic excursion at left base posteriorly less than on right. Slight dulness from 3rd rib down to base anteriorly and from 6th dorsal spine to base posteriorly. Breath sounds enfeebled over this same area, with fine friction sounds and crepitations after cough about the precordial border. Right chest apparently negative.

Abdomen distended but soft and doughy to feel. Liver dulness normal. Spleen not palpable. Movable dulness in both flanks shifting on movement of patient, with tympanites centering about the umbilicus. Fluid wave present. No rectal abnormalities or diseases.

Technique of Operation: The technique followed was essentially that used by Stewart and Stein for pneumoperitoneum. The patient was prepared about eight hours before operation by catharsis, castor oil being used, and simple enemas till clear just immediately preceding operation. The patient was also requested to omit the meal preceding the operation. At time of operation the patient was catheterized or was asked to empty the bladder by voiding and was placed on table in horizontal position. The abdominal field was sterilized with iodine and the point selected for puncture frozen by local application of ethyl chloride spray. A sterilized number sixteen gauge trocar and cannula was inserted about one and a half inches below and to the left of the umbilicus. The trocar was removed and fluid allowed to flow from the abdomen into sterilized containers. The flow may be hastened by manual compression of the parietes and inclination of table to an exaggerated Fowler position.

After all the fluid was removed the small (size B) oxygen cylinder with suitable lengths of sterilized tubing was connected with a wash-bottle containing sterile water and thence to the cannula. The current of oxygen was previously regulated by noting the number of bubbles through the wash bottle. The oxygen was allowed to enter the abdomen, with the patient in the horizontal position, to a point of goodly dome-shaped distention, which was sufficient to obliterate liver dulness. Should the pressure become excessive, as evidenced by increased rate of flow of bubbles through the wash-bottle, the rubber tubing connections will be blown off of wash-bottle or cannula; thus

acting as a safety valve and only causing temporary delay in replacing these and re-regulating the oxygen flow. The cannula was withdrawn when the filling was complete, as evidenced by dome-shaped distention and subjective feelings of patient. The wound was dressed with sterile gauze in the usual way.

X-ray pictures of the abdomen can be taken preferably within an hour or two of the operation in the postero-anterior position and the lateral or any other desired positions.

FIG. 1. APPARATUS USED BY AUTHOR

Showing trocar and cannula inserted into end of oxygen delivery tube

In four to five days, according to the rate of re-accumulation of fluid and the patient's general condition, a refill is made exactly as above described for the original operation. A new point of puncture should preferably be chosen. The process is thus repeated until the fluid fails to re-accumulate. Generally three to four treatments or more are necessary to bring about the desired results. After each fill the patient generally feels improvement after the first twenty-four hours and looks forward with great hope of relief to future treatments.

Operation: On October 27, 1922, under aseptic precautions, according to the above described technique the patient's abdomen was pierced by the trocar and cannula about 1.5 inches to the left and below the umbilicus.

Approximately 40 to 50 cc. of clear amber fluid was withdrawn. After several attempts to remove more fluid, no more would drain out and oxygen was injected through the same cannula until the patient complained of discomfort from gas distention and liver dulness was obliterated. X-ray pictures were taken within one hour after inflation in both prone and lateral positions. Four hours later he was uncomfortable and complained of pain in the abdomen; was nauseated and unable to retain liquid nourishment. The following day he felt quite comfortable and retained liquid diet. The oxygen injected into peritoneal cavity was being gradually absorbed. On the third day after operation he felt comfortable and partook well of liquid diet. Abdominal distention was still present and tympanites quite marked with movable dulness in flanks. Previous nausea and inability to retain food which was present before inflation had disappeared. On November 1 the abdomen was distended and very tympanitic: patient complained of constipation: turpentine and magnesium sulphate enema given with fair result. On November 2 he spent an uncomfortable night: complained of tympanites: passed large stool this morning which caused distress, after which felt comfortable again.

On November 5, after several more days of discomfort and some vomiting, the peritoneal cavity was again tapped as above, inserting the trocar an inch below previous puncture point. Approximately 2500 cc. of clear amber fluid were withdrawn with great relief. No ill effects followed oxygen inflation, which was performed as above, until the patient experienced a feeling of distention and liver dulness was obliterated. By auscultation oxygen could readily be heard entering the abdomen. No ensuing nausea, vomiting or insomnia. X-ray picture taken as before.

The patient felt very well after this inflation, and on November 9th oxygen was again given intraperitoneally after drainage of clear amber fluid amounting to about 60 cc.

He continued to do very well and on November 18th the treatment was repeated. At this inflation only about 30 cc. of clear amber fluid was removed.

By the end of November the patient was up and about the ward. He felt normal again in every way. His weight was about the same as when he entered the County Hospital for treatment, and he was transferred back to Muirdale Sanatorium for further rest treatment.

COMMENTS

Oxygen inflation of the peritoneal cavity was first used for diagnosis in 1902 by Kelling. In 1913 Godwin, after four years' experience with oxygen inflations following coeliotomy in tuberculous (ascitic) peritonitis, noted the nonrecurrence of the condition in patients so treated and was astounded that such a promising procedure was not

more generally used. In 1913 Bainbridge described two methods of using oxygen after coeliotomy and recommended its use for the following purposes: (1) to lessen shock, (2) to overcome negative pressure after removal of large tumor, (3) to prevent adhesions, (4) for effect on certain types of tuberculous peritonitis, and (5) for effect on pus-producing bacteria and their toxins.

Stewart and Stein gave great impetus to pneumoperitoneum as an aid to X-ray diagnosis in 1919, and it was during the course of their work that Stein noticed the favorable results in cases of tuberculous peritonitis with ascites.

More recently, Sante reported its successful use for diagnosis in 175 cases. He emphasizes the safety of the method and asserts that most of these cases were inflated by internes just out of college, without previous experience in this technique. Auscultation, as advocated by him, did not prove as satisfactory, when oxygen was used, as in the procedure for diagnosis, when air was forced into the peritoneal cavity under the greater pressure of an aspirating syringe. However, the practice of auscultation is a help in the avoidance of subcutaneous emphysema.

Shoulder pains occurred to a slight extent after two refills and were quickly relieved by elevating the foot of the bed. This phenomenon depends on diaphragmatic irritation, as shown by Capps.

Temoin reports 80 per cent cures in this form of peritonitis by coeliotomy, supplemented by exposure of the opened peritoneal cavity to sunlight at the time of operation. It is evident, by the method herein followed, that heliotherapy plays no part in the cure and that the above conclusions, as to the good effect being due to sunlight, are erroneous. It has been known for years that simple abdominal section produced good results in about 50 per cent of cases, but that in an equal number of such cases the condition was unaffected or recurred. The apparent uncertainty of the end results of coeliotomy, coupled with the fact that it is a major operation generally done under ether anaesthesia, with resulting postoperative sequellae, would naturally cause any patient to prefer the method as advocated by Stein, in which anaesthesia is unnecessary and the procedure simplicity itself, capable of repetition with little discomfort to the patient until a cure is effected.

In the matter of the time necessary to complete the cure, this method generally excels all others, such as surgery, heliotherapy and X-ray. Thus it seems *par excellence* the procedure of choice in all such cases.

SUMMARY

1. A case of tuberculous peritonitis (ascitic form) is reported successfully cured by intraperitoneal inflation of oxygen after the method of Stein. So far as known, this is the second report on this procedure.

2. The simplicity of this method, ease of performance, and freedom from danger to the patient commend this treatment in this affection above all others.

3. This method disproves apparently any important effect of heliotherapy on the exposed peritoneal surfaces in the surgical treatment of these cases by coeliotomy.

4. It affords opportunity of studying the effect of gas inflations of the peritoneal cavity, besides familiarizing the profession with this useful method of diagnosis in obscure abdominal conditions, when not contraindicated.

5. With this method it is possible to repeat inflations until cure is established, whereas coeliotomy will probably be allowed only once by the majority of patients.

6. It opens opportunity for future research in the treatment of this affection with other gases, to ascertain if the virtue of treatment lies in compression or in therapeutic effect of certain gases, as oxygen or air.

7. It is the operation of choice for a patient, especially if he be already partly exhausted by tuberculous disease in other organs; and it offers as good a prospect of ultimate cure as any method so far recommended and within as short a period of time; thus competing with coeliotomy, X-ray and heliotherapy as an established method of treatment.

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PNEUMOPERITONEUM IN THE TREATMENT OF TUBERCULOUS PERITONITIS

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It has long appeared to me that the excellent results, obtained by simple laparotomy in the exudative form of tuberculous peritonitis, might well be had without subjecting the patient to even the moderate risk and suffering incident to surgical operation. This feeling has become all the stronger since the very extensive use of air in the pleural cavity has established its relative innocuousness.

It seems that there could only be two factors entering into the therapeutic effects observed as a result of laparotomy; one, the mechanical disturbance incident thereto, and the other, the chemical effect produced by the presence of air or some of its components. It is true that a third factor has been considered by some; namely, the effect of light, either as a result of its ultraviolet or its actinic rays. In fact, in Eiselberg's clinic in Vienna, some years ago, they occasionally deliberately exposed the abdominal contents to the sun's rays for one-half to three-quarters of an hour, in order to further this effect. However, it seems extremely improbable that this short exposure could have had any material influence, except possibly to have enhanced the mechanical effect of increasing the congestion, which occurs in exposed viscera. As to the possible beneficent effect of mechanical disturbance, there is much to be suggested by the results obtained by the Talma operation, and more recently by simple exploratory laparotomy in intestinal tuberculosis, uncomplicated by peritonitis.

There is also much evidence to support the view that simple trauma may, in certain instances, favor the healing of sluggish tuberculous processes, as well as inhibit the lodgment or progress of the tubercle bacillus. For instance, it is not unusual to have a tuberculous patient make his first substantial improvement immediately after a mechanically unsuccessful artificial peumothorax, certainly suggesting that we have initiated some favorable process by means of the trauma that has been produced by our attempted collapse.

The experimental work upon rats carried out by Peschman and Corper (AMERICAN REVIEW OF TUBERCULOSIS, May, 1917, i, 165) tended to show that no favorable influence was produced by injection of air, but it did not seem to me that the conditions were at all comparable to the clinical conditions under consideration.

On July 10, 1920, there came under my care a physician from an adjoining state, who was suffering from tuberculous peritonitis with marked exudation, with the following history:

Chief Complaints: Marked abdominal distress with distention, moderate cough but slight expectoration, tires on exertion, weak, dyspneic, and slightly orthopneic.

Family History: Good except that a brother died of Addison's disease.

Past History: Always strong and never had obstinate colds or coughs.

Present Illness: In October, 1917, while with the A. E. F. in France, had marked abdominal distress, with some nausea and very occasional vomiting, which grew gradually and intermittently worse for six weeks, when he was sent to a base hospital, where chronic appendicitis was diagnosed and the appendix removed. He was then much better for a few months, after which he began to have much the same symptoms again, although not so severe as before and these have persisted off and on ever since. In September, 1918, he had influenza of moderate severity, some cough persisting for several weeks. In December of the same year, "grippe" followed by cough, which persisted somewhat to the present. He gradually grew more tired and had more abdominal distress, not distinctly related to meals. These grew worse in 1919 but he continued to work until he came here July 10, 1920.

On arrival, temperature was running 99.5° to 101.8°, pulse 95 to 110, weight 156 (normal 170), marked abdominal distress, weak, dyspneic, orthopneic, moderate cough, but only slight frothy expectoration, which was free from tubercle bacilli. *Blood:* Haemoglobin 95 per cent, polymorphonuclears 64 per cent, lymphocytes 30 per cent, large mononuclears 5 per cent, eosinophiles 1 per cent, leucocytes 7,800. *Urine:* 1018, acid, albumin negative, sugar negative, indican abundant. *Blood pressure:* systolic 118, diastolic 75.

Examination revealed a well developed and fairly well nourished man, dyspneic on exertion, slightly orthopneic, complaining of marked abdominal distress and distention, and moveable dulness with fluid wave was made out in the abdomen. Lungs showed weakened vesicular murmur almost everywhere, some increase in root dulness posteriorly extending toward apex on the right side; atypical, more or less crackling râles above roots and increasing toward bases, lung resonance ceasing one rib higher than normal on passing downward, and pulmonary resonance only very slightly moveable on either side.

The X-ray showed the heart rounded and slightly high, thickening about the lung roots with an extension in every direction, more particularly upward, which would make one suspect it was being the beginning of acute pulmonary tuberculosis.

Gastrointestinal examination showed a small fish-hook type of stomach, only moderate peristalsis, pyloris up under right costal arch, cap apparently negative, stomach emptying normally, stasis in cecum and ascending colon at the end of 24 hours, marked tenderness in that region, but no filling defect.

Diagnosis: Pulmonary tuberculosis affecting both lungs, probably a bronchogenic spread from the root; tuberculous peritonitis with effusion.

Four days after examination 6 litres of yellowish fluid was withdrawn from the abdomen, followed by considerable relief but by rapid refilling. Five days later 4 litres was withdrawn and 1500 cc. of sterile filtered air introduced by means of an artificial pneumothorax apparatus. This was followed by considerable abdominal distress, especially on turning or rising. This persisted more or less but gradually diminished. At the end of a week another litre was withdrawn, and 500 cc. of air introduced. Distress, this time, was not so marked and there was no appreciable reaccumulation of fluid. The temperature, which was running 99.5° to 101.8°, came to normal within two weeks of the first introduction of air and remained practically so.

Three weeks after the second introduction of air, no definite fluid or air could be made out, but there was fairly marked general tenderness over the abdomen. Gastric symptoms rapidly disappeared and there was rapid gain in weight. On September 28, 1920, it was noted that there had been no fever for seven weeks, no cough nor expectoration, the patient was looking well, and he said that he had not felt better for years. The lungs, aside from the few root signs, were negative.

He returned home in October, 1920, three months after coming to Colorado and gradually resumed his usual work. He returned for examination six weeks later, reporting that he felt well except for soreness in the abdomen, when he was on his feet too much. He had no fever, cough or expectoration, and had gained ten pounds more. The abdomen still showed slight general tenderness, but no dulness or distention. The lungs still showed slight increase in root dulness on the right, with harsh breathing above, but no râles.

July 1, 1923, he reports that he has now been in active practice for two and three-quarter years and seems to be perfectly well except that he tires a little easily, but has no abdominal symptoms, and no cough nor expectoration.

At the time of beginning the treatment of this case there were no reports of the method ever having been used clinically; but we were familiar with the experiments of Peschman and Corper mentioned above. However, on making a survey of the literature we find the

records of several cases which have since been treated and reported, that of Stein being the only one reported from this country; in his case oxygen was used, while in ours filtered air was used. The following list includes articles that have appeared in the literature to date:

Oxygen inflations of peritoneal cavity in tuberculous exudative peritonitis, Arthur Stein, J. Am. M. Ass., 1922, lxxviii, 718.

Therapeutic pneumoperitoneum in tuberculous peritonitis, Sorgan and Frits, Med. Klinik, 1921, xvii, 1513.

Therapeutic pneumoserora in tuberculous peritonitis, P. E. Weil and J. Loileseur, Bull. e. mem. soc. méd. d. hôp. d. Par., 1921, xlv, 1661.

Pneumo-peritoneal roentgen ray diagnosis, A. Stein and W. H. Stewart, Southworth Publishing Co., Troy, N. Y., 1921. Oxygen or air for therapeutic purposes, pp. 57–66.

December 22, 1923: Since writing the above article the author has treated the following additional case with pneumoperitoneum.

Joseph C., 18 years old, male, schoolboy, born in Colorado of American parents.

Chief Complaints: Fever, headache, weakness, nausea and distention of abdomen.

Family History: Parents came to Colorado shortly before birth of patient, on account of pulmonary tuberculosis in the father, who improved and a year later returned to Nebraska where they lived until about three years ago.

Past History: When two and a half years of age patient fell from a porch, striking on his back, and not long afterward spinal curvature was discovered, and he was kept in a plaster jacket for about a year, and seemed to recover except for the kyphosis, which remained, although he became a fairly normal, active boy, but of slightly stunted growth. In April and May, 1922, he passed through an attack of acute nephritis, but after two months became as well as before, although his urine still showed occasional slight traces of albumen and a few casts up to May, 1923.

Present Illness: Early in July, 1923, began to have malaise and restlessness, with some fever, headache, general aching, constipation and pain and tenderness in the lower abdomen. He was seen on July 13th by Dr. W. K. Reed. There was a continuation of above symptoms with temperature of 103.2°, pulse 108, respiration 26; urine, negative. On July 20th condition much the same; Widal negative; leucocytes 9,600; urine showed a slight trace of albumen, but was otherwise negative. Abdomen was more distended and patient was short of breath. On July 23rd, fever continued high, with only slight morning remission. Abdomen still distended; patient complaining of pain in the knee; heart and lungs negative.

When seen by the author on July 25th, 1923, general condition was as stated above, with temperature of 104°, pulse 120, respiration 28. There was moderate pallor with a suggestion of cyanosis, very moderate dyspnea, head supported by two pillows, knees inclined to be drawn up. Reflexes and pupils negative. *Heart:* apex in 4th space just outside nipple line. Lungs negative except for a moderate number of crackles at bases. Moderate kyphosis at the 7th and 8th dorsal vertebrae (no doubt tuberculous), but no evidence of active trouble there. Abdomen rather markedly distended and fluid wave elicited. Rather marked tympany in neighborhood of umbilicus, but marked dulness in the flanks. This shifted with change in position, the uppermost parts becoming tympanitic and the lowermost dull.

A tentative diagnosis of tuberculous peritonitis was agreed upon. The next day a small trocar was introduced and 2500 cc. of fluid was withdrawn. A pneumothorax apparatus was connected, but no readings could be made on account of the tube filling with fluid. While this was still attached 1200 cc. of filtered atmospheric air was introduced and the trocar withdrawn. The patient experienced much relief from the distention and complained only slightly of the presence of the air (as it gurgled about when he would turn), but there was no complaint of this after twenty-four hours. Temperature dropped to 99° within forty-eight hours and remained in that neighborhood for two weeks, after which it was normal until in September, when there was a rise to 100°, with some atypical signs about the roots of the lungs; but these persisted for only about a week, after which the temperature came to normal and has remained so. The fluid removed was exudate and, inoculated into a guinea pig caused generalized tuberculosis.

On August 17, 1923, a second paracentesis was done, but only 500 cc. of fluid was obtained and 300 cc. of air were introduced. Since that time there has been no evidence of fluid in the peritoneal cavity. After the second aspiration the patient was put upon heliotherapy as well as could be done at home, but only succeeded in getting a moderate amount of pigmentation. On November 7, 1923, he was removed to Mesa Vista Sanatorium where natural heliotherapy was supplemented by the mercury-quartz lamp and he is now getting a good coat of tan.

Examination at this date shows heart normal, lungs normal except for a few basal crackles. Temperature is normal except for a rare 99°, pulse 75–90. Gaining in weight. Abdomen negative except for slight general tenderness.

May I further add that since writing the above report I have learned by way of personal communication from Dr. Ernest S. Mariette of Glen Lake Sanatorium that he used this method on a case in 1918 but was compelled to supplement it by heliotherapy and abandoned the method for the latter as being more effectual.

SURGICAL AIDS IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

PHILIP KING BROWN

San Francisco

Wilfred Grenfell tells of an Esquimau boy on whom he had done a thoracoplasty, and how, after the period of convalescence, the boy had attached himself to a powerful but blind Frenchman and the two were retained as workers about the picturesque settlement, probably doing as a team as much work as any two well persons could do. It took Grenfell and his wonderful spirit, his skill as a surgeon and his economic sense, to work out, to an ultimate complete solution, this tragic human problem;—a hopelessly advanced consumptive, a brilliant surgical relief, and a real job for the cured but handicapped boy. It is an example of Grenfell's modesty that in the face of his great achievement he emphasizes his pleasure in seeing "the joy of victory" in the features of the blind man, "the triumph of the man over the pitifulness of his sightless eyes," when it must be quite plain that the real triumph lay in the inspiration of his own spirit and vision and his skill as a surgeon.

Those of you who have watched the long tiresome struggle of so many consumptives,—postponing return to active life year after year, creeping inch by inch toward the goal of health, only to slip back yards at a time, often to death because of a hemorrhage or relapse, invalided by secondary involvements of other parts or intercurrent troubles which beset them, all too few reaching again economic efficiency,—you realize that the two great problems of tuberculosis, apart from prevention, are early recognition of the disease and far more active treatment for cases that do not do well on the routine of good medical guidance, rest and the usual hygienic and helpful surroundings, and who present at some time in their course the largely unilateral involvements which we are learning to deal with by surgical means. With better histories, better studies and interpretation of progress or retrogression, better and more frequent X-ray plates, and the amazing

[1] Read at the annual meeting of the National Tuberculosis Association, Santa Barbara, California, June, 1923.

advances of surgery of the lungs, it seems likely that more cases all the time may be removed from the expectant-care method and be assisted toward permanent relief by more active measures.

The most signal recent contribution to the therapy of tuberculosis has been the improvements in methods of bringing about rest of the actively diseased area; for it is rest alone that has stood the test of time in the treatment of the disease. Of the surgical means of producing rest, artificial pneumothorax has the widest application and it is unquestionably the greatest modern achievement. The chief trouble with it is that it is a method that must be used under conditions that admit of the most intimate study of what is accomplished by each compression. Not only should cases be examined by X-ray before and after air is introduced, but whenever any question arises stereoscopic plates ought to be made, so that the most accurate interpretation of conditions may be obtained. Blindly putting in air to neutral pressure is as stupid as pouring a measured amount of water in a rat-hole. Any use of pneumothorax uncontrolled by fluoroscope and plates is going to do harm and is not scientific. It has already brought the method into ill repute and such use of it should be condemned. There is no question in the world that pneumothorax must be tried for unilateral infection in which there is cavity of any considerable size. There are cases (figs. 1, 2, 3 and 4) in which, after many years, although the heart may be pulled over from the left to the right side and the shoulder pulled forward and the diaphragm raised, there is still a cavity to deal with, and the constant danger that the whole process may again light up. There is no question that it is justifiable to take desperate means to close such cavities, and the first of these is artificial pneumothorax. I do not consider it necessary to argue the case for pneumothorax, but I do think it is necessary to state emphatically that the neglect of cavities, which I see so constantly, and the continuance of sanatorium care for cases that never had the slightest chance of closing cavities unassisted, are bad practice.

It is probably justifiable in some cases in which the process is more active on one side, and in which any assistance making for abatement is desirable, to resect the phrenic nerve on the more advanced and active side. It cannot be of any very great assistance; but any assistance obtained at no great cost or exposure to the patient is not to be refused. There is some reason to believe that the sucking action of the diaphragm may make this procedure desirable, as it stops that

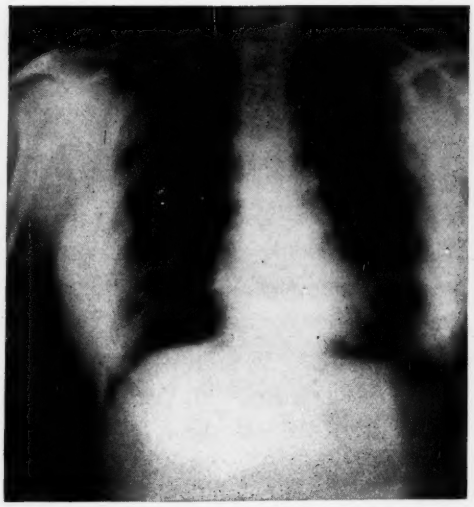

FIG. 1. CAVITIES, MAY, 1914

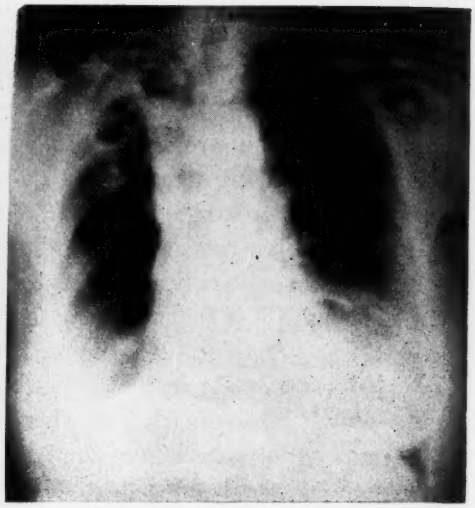

FIG. 2. SAME CAVITIES, OCTOBER, 1922, SHOWING INEFFECTUAL EFFORT OF NATURE TO CLOSE THEM

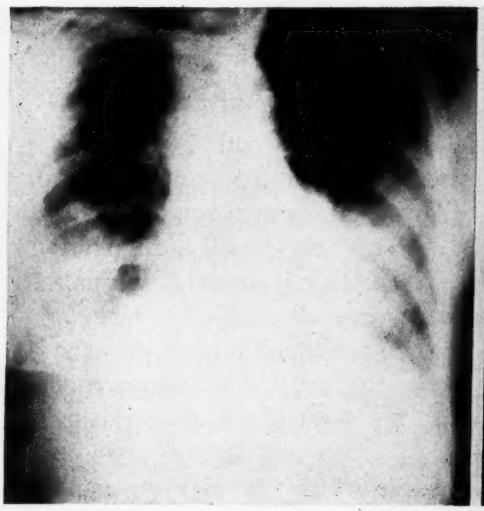

FIG. 3. MULTIPLE CAVITIES IN RIGHT LUNG, MARCH, 1917

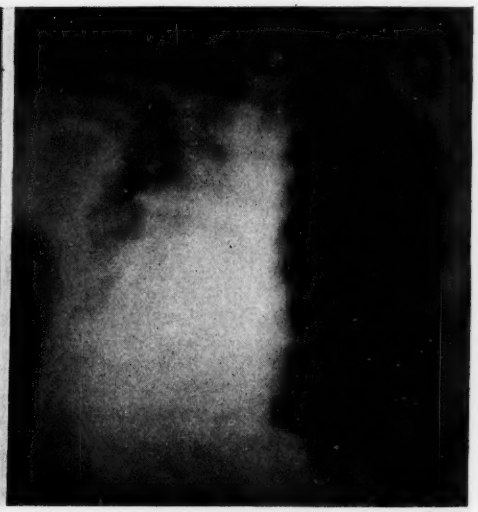

FIG. 4. NATURE'S EFFORT AT CLOSURE, ASSISTED BY UNSUCCESSFUL ARTIFICIAL PNEUMOTHORAX, FEBRUARY, 1922, FIVE YEARS LATER

Heart pulled over to right side. Compensatory scoliosis. Right diaphragm raised. Cavity still present.

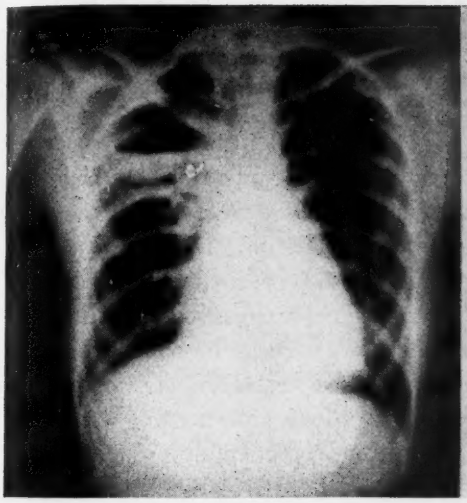

FIG. 5. LARGE CAVITY AT RIGHT APEX, ONE-THIRD FILLED WITH FLUID

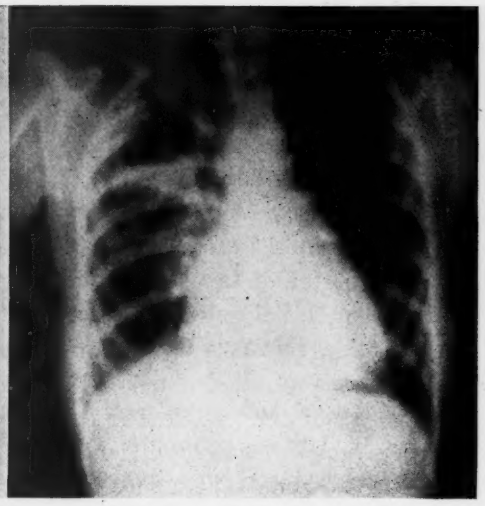

FIG. 6. SAME CAVITY AFTER THREE INJECTIONS OF 400 CC. OF AIR EACH

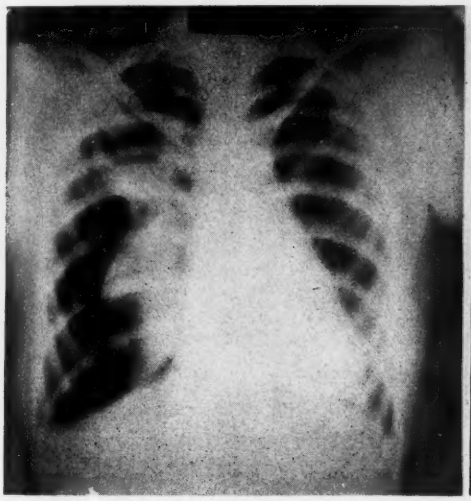

FIG. 7. SAME CAVITY AFTER FIVE MONTHS OF COMPRESSION

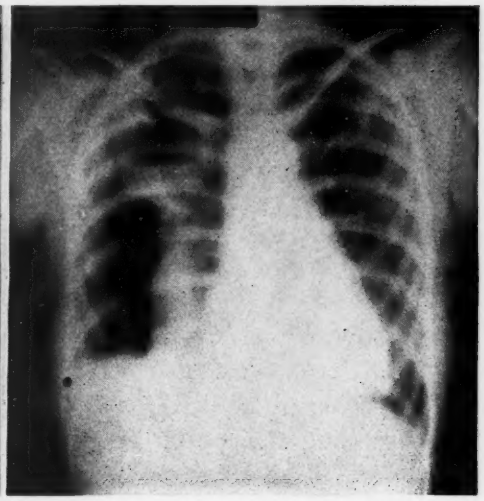

FIG. 8. SAME CAVITY AT THE TIME SURGICAL INTERFERENCE WAS RECOMMENDED TO SECURE COLLAPSE

action in cases in which thoracoplasty is to be tried for cavities in the upper lobe. There is not on record enough experience on cases that have been carefully worked out to permit me to be very positive about this procedure, which is in the stage of trial and in which it is hoped that the results of the trial will be very carefully worked out. Finally, it so often happens that cavities cannot be closed because they are held open by adhesions (figs. 5, 6, 7 and 8), which cannot be stretched or broken by air compression; or there may be complete obliteration of the pleural cavity, so that air cannot be used at all, and some way must be found to put the underlying lung at rest. The present difficulty of this situation lies in the fact that lung surgery is more or less recent in this country and that rather hopeless cases have been the only ones afforded a trial of this method. The test has been a very severe one and yet, in our experience, it has done so much for otherwise hopeless cases, that we are presenting some results obtained, with the hope that a more widespread interest in the procedure may follow.

If the logic of the procedure be followed up and the advising physician feels justified in doing artificial pneumothorax, and for any reason the latter should fail, a thoracoplasty is certainly in order on the same grounds that justified the attempt at pneumothorax. The wrong in the situation, if there be one, lies in leaving the condition to be dealt with surgically as a last resort.

THE HELIOTHERAPY OF TUBERCULOSIS

A. ROLLIER

Leysin, Switzerland

Medical men the world over have lately shown a quickened interest in sun-cure, and this not only because of the general recognition, based upon an increasingly accurate apprehension of the nature of tuberculosis, of a method that has proved itself efficacious, but also because, the fight against this disease having become a social question in every civilized country, the special value of sun-cure demands the attention of all those engaged in the struggle. The terrible havoc wrought by this scourge among people of all nations has aroused a spirit of enquiry and all that may tend to the elimination of the disease has become of supreme importance.

Internal and external tuberculosis are not only local ailments but must be regarded as manifestations of a general infection, which produces local symptoms and makes its appearance in local seats of disease. The therapy employed must give a general effect and completely restore the patient's normal constitutional condition, and this must be coupled with a rational local treatment which will never hinder but rather promote the necessary rebuilding of the whole system. It was with this end in view that, in 1903, we opened the first clinic for air-cure, combined with systematic heliotherapy at a high altitude in Leysin, a village of the Swiss Alps, that stands 4,500 feet above sea-level.

From the earliest beginning of our work we have advocated an open-air life for our patients, combined with complete sun-baths; that is to say, the action of the sun over the entire surface of the teguments, an action that constitutes the most energetic of excitants and tonics. Heliotherapy realizes also the necessary, coincident local treatment, adding to its reconstructive powers the analgesic, bactericidal, sclerogenic and reducing effect of the solar radiations.

Sun-cure may be applied wherever the sun shines,—at sea level, by the seaside, in the mountains. If we have chosen to erect our clinics at a high altitude, it is because here we are aided by the tonic effect of

the Alpine air, where the climatic conditions are such that sun-baths may be taken all the year round, thus permitting an uninterrupted cure and the maintenance of the body at its maximum vitality and power of defence.

What is the action of the sun on the organism? This is one of the most captivating questions now asked of modern science, and its answer could only be very imperfectly outlined even in a long lecture. The space at my disposal only allows me to make a very limited survey on this part of our subject. In the first place, we must ask you to bear in mind the double action of light on the body, its direct and its indirect action. There has been a long-standing doubt as to this direct action, for the bactericidal violet and ultraviolet rays have only a superficial effect. However, the work of Wiesener has proved that the infrared rays, and more especially those near the red, are also bactericidal, and, by means of their long wave-length, can penetrate the body and may thus have an action on coming in contact with deepseated lesions. But if the direct action of sunlight is still matter for discussion, the capital part it plays indirectly has been proved by numerous experiences of which we can here give only a very condensed account.

We all know that the violet and ultraviolet rays, held at a depth of 1 millimetre in the skin, are absorbed by superficial sanguine surfaces formed by the network of capillaries dilated by the sun. It is to the action of those rays that we must attribute the phenomena of erythema and pigmentation.

Pigmentation not only gives protection against the too violent irritation which might be provoked by the ultraviolet rays, but it also regularizes the action of the thermic part of the solar spectrum. The profound biological value of pigment is increasingly recognized by all scientists. It is very likely that pigment receives, supplies and increases the activity of the elements essential to the metabolism of the hormones. You know that Bloch has demonstrated that a substance, very much like adrenalin, submitted to the action of an enzyme of the epidermis produces the formation of normal epidermic pigments, light strongly accentuating this formation. On the other hand, these ferments of the epidermis seem to depend, proportionally, upon the quantity of vitamine contained in food, as has recently been proved by the experiment made in Vienna on rachitic and insufficiently fed children. Let us also remember that recent German and American[1] publications have

[1] See the publications of Alfred F. Hess, M.D., New York.

demonstrated that the action of radiations produces a very strong retention,—which has reached 400 per cent as a maximum,—of the phosphates and lime in the body. Let us remember, finally, that Naegeli has proved the action of sunlight on the haematopoietic system to be followed by an increase in haemoglobin, that Behring has demonstrated an increased activity of respiration in the red globules submitted to the sun, and Schläpfer has given us the proof of the photoactivity of a photographic plate, by means of its exposure to previously insolated blood. Lastly, we might mention the recent experiences of Sonne in Copenhagen, who has proved that under the action of radiations the temperature of the blood, at a depth of more than one-third of an inch in the skin, augments to about 5°C.

From these experiences must be drawn the conclusions that the light absorbed by blood changes it into a receptacle of radiant energy. Transferred into the whole organism this energy hastens the intracellular processes of oxidation and reduction, thus modifying the whole metabolism. Consequently, in this way the defense of the organism exposed to the beneficent action of the sun is progressively increased, making it better fit for the fight against tuberculous infection.

Among the general effects of sunlight on the body, we would first mention its action on the skin, and for this reason: that we attribute a capital importance, in our results, to the reconstitution of this essential organ under the influence of the sun's rays. The skin is not only the natural clothing of the body, wonderfully fitted to protect it against the penetration of pathogenic microörganisms, but, provided as it is with a compact web of capillary vessels, it forms an expansion of the vascular system. These vessels, by their contraction and dilatation, constitute a kind of "peripheric heart"—an admirable regulator of the circulation of the blood. The skin is also an expansion of the nervous system: this close-woven net of sensory and sensitive nerves may be compared to a keyboard, the lightest touch on which provokes resonances through the whole organism. The skin is not only an organ of protection, circulation and innervation, but also one of respiration and nutrition, since it gives off carbonic acid and water vapor and absorbs oxygen. Finally, the skin is an essential organ of elimination; for this reason it has been called "the vicar of the kidney" and the so called subordinate is perhaps even more necessary than its superior, for normal life may continue indefinitely after the ablation of one kidney while death ensues if even one-third of the cutaneous surface is destroyed.

Its important physiological functions can only be accomplished if the skin is placed in its natural surroundings, and air and light are as much its natural surroundings as is water to the scales of a fish. Though the wearing of unhygienic clothing has weakened and atrophied it through many generations, the skin, under the influence of sunlight, recovers the power to accomplish its many and vital functions, and becomes again the ideal covering prepared by Nature. The gradual formation of pigmentation gives the body proportionally increased resistance to cold and heat, it lessens the danger of infection for sores and wounds and it takes a large part in their cicatrization. Pigmented teguments are refractory to numerous cutaneous affections, such as furuncles, acne, etc., which often are merely doors through which more serious diseases may force an entrance.

The sun-bath, enlarging the capillaries, determines an afflux of blood toward the skin; this ameliorated and regulated circulation of the blood helps to make the musculature remarkably firmer, better than the best massage would make it; thus the body finds again its natural harmony. The tonic power of the sun manifests itself also on the thoracic and abdominal organs; under its influence, haemoglobin increases, internal secretions accentuate, digestive functions become regular, weight increases, strength is renewed. The sun acts not only on the physical side; it has a most striking effect on the mind and the character of the patients. This is of great importance when one remembers how much this influence reacts on the physical side, especially with patients who have to remain a long time confined to bed.

How must sun-treatment be dosed? The aim of posology is the solution of this problem, which is one of the most important to be considered in heliotherapy. Space does not permit of my dwelling on it as it deserves and as I should like to do. On knowledge or lack of knowledge of posology depends the result that we may expect from sun-cure; and let us bear in mind that no physiotherapeutic method demands such strict individualization as heliotherapy.

A very current mistake consists in thinking that the sun-bath is all the more efficacious if prolonged or taken when the sun is at its hottest; this is an inconsistency against which Nature herself seems to warn us. We have laid down very precise rules for the practice of sun-cure, in order to prevent miscalculations and accidents. The principal rule is this: one must begin by exposing only the lower, less sensitive parts

of the body to the sun's rays. This will serve to show in what measure the patient bears the sun-bath, and his further progress in insolation will be based on such observations. This method of derivation avoids congestion of the head and of the thoracic viscera. Air and sun-baths must never be taken during the meridian hours, especially at sea level where the ambient atmosphere tends to enfeeble the patient, produces congestion and thus annihilates the good effects of the solar rays. During the warm months of the year heliotherapy should only be practised during the early hours of the morning.

Air and sun-baths should always be taken gradually, the duration of insolation increasing by a few minutes each day, first exposing the feet, then the legs, then the thighs, the abdomen, the thorax, keeping the head covered with a simple linen hat. After a certain period of certain advance, varying according to the case, the season of the year and the heat of the sun, the body becomes pigmented and can then bear several hours of sun each day. As a general rule, the sun bath, to be beneficial, should create a sensation of profound well-being, and each patient while taking it and afterward, should find himself invigorated.

Before speaking of our technique I think I ought to give you some idea of the installations in which we practise heliotherapy. I have neither the necessary space at my disposal nor the desire to describe our 34 institutions in detail, but I should like to tell you about the first house we opened. It was then the only little boarding-house in our village; it is now one of our free clinics, opened in 1903. We fitted it up for the sun-cure by the addition of large balconies and a roof solarium, which was probably the first to be built in Europe since the time of the Romans. Here we have proved our contention that heliotherapy may be successfully applied elsewhere than in ruinously expensive palaces, for it is in this simple chalet that we obtained most of the cures which have since served as bases for all our subsequent experiences and for the photographic record of particularly remarkable cases.

It is indispensable to give in a few words the teaching of experience in regard to the application of sun-cure. We will take the different localizations in their turn, beginning with Pott's disease and the most important articulations.

As the bed plays a very essential part in the treatment of such localizations and is, so to speak, one of our principal tools, I take the liberty of insisting on some of its particularities. Its indispensable feature

are the following: It must be high, so that the balcony rails beside it may not obstruct the sun or the view, and to facilitate the nurse's work. It is fitted with large, smooth, easily running wheels, and it can be rolled on to the balcony, to concerts and even to the garden.

Special, very hard mattresses are used. These never lose their shape, give the patient's body a maximum of support, do not induce perspiration, and prevent bedsores. The spring-mattress is composed of widely spaced strips of metal, thus ensuring perfect aeration of the mattress. Very emaciated patients are padded in with cushions.

From the first we have discarded plaster jackets in our treatment of cases of Pott's disease, for we discovered that these determined a very considerable atrophy, not only of the skin and muscles but of the skeleton itself. These cumbersome plaster devices have been replaced by simple arrangements of webbing straps which give sufficient immobilization, while permitting the free access of air and sun to the injured places. Patients, especially children, are immobilized by a simple apparatus consisting of linen stays or braces, attached by means of linen straps to the head and the foot of the bed itself. These can be opened and closed at will, and cannot in any way interfere with the sun and air cure. Straps are also fastened down over the knees to keep them in position.

As soon as an X-ray examination shows the beginning of calcification of the vertebral block, the patient is placed in the ventral position, the thorax supported on a triangular cushion on which the patients can lean their elbows. To this physiological position, *par excellence*, we attribute a very great importance. This same treatment, as regards position, was advocated about a hundred years ago by two English doctors, Banting and Bamfield, and had been long abandoned when we again gave it the consideration it deserves. This position augments the lordosis and thus tends to correct the pathological curvature. It permits the insolation of the whole dorsal region and, so, very considerably develops and strengthens the muscles and ligaments.

Once cured, our cases of Pott's disease are all provided with what we call the "muscular corset," which is the best support of the spine for the future. In certain cases, in order to help the correction of kyphosis by straightening of the shoulders, we use braces which are fastened to the foot of the bed.

For hip disease we use very much the same appliances as in the treatment of Pott's disease. We have done away with the plaster apparatus in these cases also, and these clumsy splints have been replaced by a

continuous extension, obtained by attaching a sort of double bracelet, made of linen or leather, round the knee and ankle. This can be removed at will, and allows the insolation of the hip and even of the whole leg. This simple and really effective apparatus is completed by a small sandal which combats the tendency to equinism.

I wish to add that in bad cases of hip disease, complicated by a vicious position of the articulation, the double bracelets I have mentioned are not always sufficient in the way of extension and a more energetic apparatus is needed. We then apply extension by means of sparadrap. To make the tension more bearable for the patient, the leg is laid on a wheeled splint, borne on a small carriage, which rolls very easily and allows us to obtain a thorough extension while employing only a moderate weight.

Plaster splints of the ordinary type have also been discarded in cases of tuberculosis of the knee. When the knee is painful, it is placed in a widely opened splint and continuous extension is applied. The diseased limb is always supported on an inclined plane, for this position offers the most favourable condition for regression of the capsular and periarticular infiltration. The plane is more or less inclined according to the gravity of the case.

In the cases of tuberculosis of the feet we also use immobilization on the inclined plane, in little splints which are widely hollowed out, or a mobile sandal allowing the progressive straightening when equinism, as often is the case, accompanies tibiotarsal arthritis.

Heliotherapy gives the most favorable results in cases of peritonitis, but this is, of all the localizations, that which requires the most careful supervision, especially as it is often accompanied by pulmonary and pleural complications. It is quite natural that the peritoneum, which presents a great surface vascularization, should become very easily congested, and this is where our method, in French described as the "derivative method," proves itself of singular utility. It provides for a slow and progressive insolation which draws the blood down to the extremities, thus obviating the possibility of such congestion as might follow sudden local exposure to the sun.

Heliotherapy gives quite as favorable results in cases of fibrocaseous and fibroadhesive peritonitis, as well as in all forms of ileocaecal tuberculosis. The advantage this treatment has over operative measures is that such complications as formation of faecal fistulae, which are rather frequent after resection, can be avoided.

Heliotherapy is also the preëminently successful treatment for cervical adenitis, which is always cured without leaving any scars by one of the three different processes: "melting;" generally followed by aspiration; spontaneous resorption or sclerosis. The two first mentioned processes occur more frequently than the third. It is but seldom, and only in the treatment of exceptional cases of adenitis with sclerosis, that we have recourse to the association of X-ray therapy with heliotherapy. The exclusive use of heliotherapy has the advantage of never giving rise to such accidents as radiodermatitis.

Finally, we must add that heliotherapy gives the most satisfactory results in all cases of lupus.

Having explained the treatment of the different localizations, I should like to add a few words about the work-cure which was first introduced into England by Dr. Paterson at Frimley Sanatorium in the cases of patients suffering from pulmonary tuberculosis. This work-cure was started some time ago by Dr. Varrier-Jones at his wonderful Cambridgeshire Colony, and we were the first to organize it for external tuberculosis. It is now carried on in all our popular institutions for surgical tuberculosis and its results are most satisfactory. I wish to insist on this most valuable factor in the victorious conflict against mental depression and one which we consider to be a most precious adjuvant to heliotherapy. We never fail to advise our patients to interest themselves in some form of light and pleasant handicraft, and usually with the happiest results both to their moral and physical well-being.

GENERAL OBSERVATIONS

The best orthopedic and preservative surgery may be practised by means of heliotherapy; it safeguards the entirety of normal articular function, to the greatest degree possible, and to a greater extent than could be obtained by surgery, and in so doing makes the nation a gift of citizens who are neither deformed nor incomplete, but of sound bodily capacity.

Furthermore, the treatment involved is not within the reach of wealthy patients only. Indeed, it may be argued that as a cure it is economical in a social sense, since it is cheaper for a community to assure the complete fitness of one of its members, even though this

may entail a year's or perhaps even a two years' stay in bed (this time to be passed in the open air and sun) than that the inevitable mutilation attendant on an operation should lessen his value forever.

MAINTENANCE OF CURE

Clinical results obtained by the sun-cure can only be considered valuable if they are lasting. The best way for all those who have suffered from surgical tuberculosis to maintain their cure is that they should henceforth live, as nearly as possible, under conditions nearly approaching those that determined the cure. To avoid a relapse an ex-patient must neither take up an unhealthy occupation nor reënter an unsanitary lodging, but rather choose a trade or profession that promises reasonably healthy conditions of life.

To this end we have recommended and set on foot a market-gardening colony and an agricultural colony for our convalescent patients. The results from the double standpoint of capacity for work and resistance of the constitution have been decidedly favorable. Efforts should be made to extend these settlements, for it is of first importance to solve the great problem of the maintenance of the cure.

It has often been said that the cures effected by heliotherapy are not lasting. We are now establishing records with a view to the publication of early cures. This task presents many difficulties, the majority of our former patients having been foreigners, who are not easy to trace through the chaos that obtains in many European countries since the war. We had however the good fortune to receive new corroboration, and illustrated by photographs, from some of our first cases, which have been mentioned in previous publications; and we can now show a number of these patients, some ten, twelve, fourteen and even more years after the establishment of their cure. This is all the more striking, judged as a result, because all these patients were poor folk, or at least ill-provided with this world's goods, and since leaving Leysin they have been obliged to work for their living.

It has often been said, and is still believed by many, that heliotherapy is dangerous, and its application powerless to help in cases of pulmonary tuberculosis. We hold a different opinion and our experiences tend to prove our contention. It is true that most of the cases that we have treated accompanied surgical lesions. By careful examination of the lungs of our surgical cases we discover that about 30 per cent of them

have pulmonary foci as well. We have, however, also had in our care a whole pavilion of Swiss soldiers with pulmonary tuberculosis only, and we have never met with an accident of congestion, and no soldier who has been treated by sun-baths has ever presented manifestations of haemoptyses any more, even if subject to them previously.

So we are convinced that the sun is not an agent of congestion, but rather a derivative, and might be compared to a cupping glass, the action of which we can regularize. It must, however, be well understood that the sun-treatment in such cases must be applied exactly according to our derivative method; that is to say, by always beginning by the exposure of the extremities, and proceeding by prudent and slow progression. The sun should be dispensed, so to speak, drop by drop, when nearing the region of the thorax. It is also essential, as we have always said, that the heat of the midday hours should be avoided for the treatment, and one should have recourse to the earliest morning sun, while the air is not yet overheated.

Needless to say, no patient with a high temperature, nor one who is passing through a period of acute evolutionary intoxication should be exposed to the sun.

If these photographic documents bear testimony to the success of heliotherapy, the demonstrations given by the X-rays which are taken regularly of each patient, and the number of which now attains the total of 13,000, are much more convincing, and show with admirable clearness the process of cure of the most deepseated lesions in the skeleton, a process which in many cases goes as far as to reconstruct it *ad integram*.

If sun treatment can cure so many manifestations of tuberculosis and maintain this cure, it can all the more prevent its outbreak. Experience confirms this. The sun-bath, associated with open-air life and rational exercises, is the most active and surest prophylactic means, and for this reason acquires a social value surpassing its therapeutic value.

According to present views, it is granted that tuberculous infection occurs, as a general rule, during childhood; reaching the age of puberty, nearly all children (95 per cent) have paid a debt to tuberculosis. Adenopathic and mesenteric ganglia are as outposts, where tubercle bacilli are kept in check. Since the germ of the disease is caught during childhood, it is during that same time it must be fought and overcome. Tubercle bacilli are incapable of harming so long as the bodily organism

is fit to withstand. There is no surer way to attain this state of resistance than by air and sun. That is why, from the first, we have pleaded for its application in nurseries, orphanages, and holiday schools; for in the schools, where constant discipline is the rule,—dicipline so often absent from family education,—these principles of hygiene can be applied to children with most profit.

We have put into application this prophylactic means with delicate children and those predisposed to tuberculosis in our *School in the Sun*, established at Cergnat in 1910. Instead of educating children in rooms more or less without air and light, lessons are given them in open air and sun; this continual open-air life soon completely transforms the children; weak, ailing little beings, a prey to illness, become vigorous, bronzed children, with good musculature and fit to withstand fatigue and inclemency of weather, strongly protected against tuberculous invasion.

We know that hygiene is well applied in the schools of the United States, and the important part it plays in your open-air schools particularly. Our only suggestion would be that a larger place should be given to the sun, so as to place the children's bodies as much as possible in contact with the solar rays, at least during the gymnastic exercises.

This method could, without expense, be widely applied in all the schools. The beautiful parks and public squares, the glory of your country, would also be a splendid field, even if they were only used one or two hours a day for physical exercise in the sun.

"Where the sun enters, the doctor does not go" is an old saying that contains a rule of life that should prove very valuable in its application. Sun is indeed the sovereign remedy that a farsighted Nature has placed within the reach of us all. It behooves us to make the most of it. The human body, everlastingly threatened and besieged by many evil forces, must be constantly and effectually armed against them. Let it demand of sun and air, these fundamental elements of hygiene, the force of resistance of which it stands in need.

These elements should be given a larger place in our daily lives and in the organization of our cities. Not only modern towns, but the homes of which they are composed, should be constructed on hygienic principles. Defective housing has played an immense part in the genesis of child and adult tuberculosis: the community bears the responsibility of the waste of human lives due to insanitary houses. These

principles should be spread everywhere among all classes of society, that all may be fully persuaded that they contain a guiding principle to the conditions indispensable to health and life itself.

For statistics see *Heliotherapy*, by Dr. Rollier (Oxford Medical Publications).

Recent statistics can be found in Dr. Mathieu's thesis: *L'importance de l'héliothérapie à l'altitude dans le traitement de la tuberculose et spécialement de la tuberculose chirurgicale.* (Maloine, Paris).

LIGHT ENERGY IN THERAPEUTICS[1,2]

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As a therapeutic agent sunlight has been extensively used for a number of years. Its value in the treatment of disease has been definitely established, yet in spite of its wide use and acknowledged virtue little is known of its action. The experiments conducted and the clinical observations that have been made have only brought forth contradictory conclusions.

Various theories regarding its action have been suggested. Those who attributed to one portion of the spectrum greater beneficial value over other portions have tried to substantiate their theories by the use of lights rich in that particular ray. For instance, the theory that the short wave-length end of the spectrum is the beneficial part has been tested by the use of the Alpine sun lamp, which produces more ultraviolet rays than are ever present in altitudes where suncure might be given. Some of these wave-lengths are not present in sunlight; and it was found that, owing to their extreme chemical activity, they were detrimental, leading quickly to degenerative changes, and so were unsuitable for therapeutic purposes. DuPan found it necessary to exclude portions of these rays in using the Alpine sun lamp. On the other hand, if we hold the view that all the rays of the sun have a part in its beneficial action, we see the necessity of finding a source of artificial light that is as nearly as possible an exact duplicate of natural sunlight, both in quality and relative proportion of rays produced. The nearest approach to the light of the sun is the carbon arc lamp; but, while its spectrum closely resembles that of sunlight, it falls far short in the number of rays produced, except in the ultraviolet and infrared portions. It must be admitted that the results obtained by artificial means are not comparable with those ob-

[1] From the Department of Research of the J. N. Adam Memorial Hospital, Perrysburg, New York, under the supervision of John H. Pryor, Consultant-in-Chief, and Horace LoGrasso, Superintendent.

[2] Presented in abstract before the American Sanatorium Association, Perrysburg, December 9, 1922, and the Buffalo Academy of Medicine, May 9, 1923.

tained by solar radiation, and that none of the substitutes tried thus far have been entirely satisfactory.

It may be true of the human body, as it is of plant life, that different cells respond to different rays. If this theory were proved, the beneficial effects of sunlight might be easily explained. It would also be quite clear why natural sunlight, with its complete range of rays, has given more satisfactory results than less complete artificial lights.

PHYSICAL PROPERTIES OF SUNLIGHT

Sunlight may be defined as that form of energy which is emitted by the sun, acts on the organs of sight and has the three properties of heat production, light production and chemical action.

The rays radiated by the sun travel in straight lines and are propagated at the same velocity, but they vary in wave-lengths. This difference in wave-length manifests itself to our eyes as color. These rays may be separated by passing sunlight through a prism, which will refract and disperse them into a series of colors ordinarily described as the visible spectrum, and composed of red, orange, yellow, green, blue and violet. There is also an invisible spectrum, composed of the infrared rays below the red region and the ultraviolet rays beyond the violet. All of these rays are capable of heat production, light production and chemical action, and it is best to think of them in this manner, rather than dividing them into heat-producing (red), light-producing (yellow), and actinic (violet), as they all possess these three properties and are identical except in rates per second and distances apart.

The capacity to transmit light varies greatly in different bodies. Those that transmit it freely are transparent while those that intercept it are opaque. Opaque bodies are of two kinds; those that turn back the light at the surface and those into which the light penetrates and is absorbed and transformed into heat.

The amount of light reflected by an object depends to a large extent upon its color. The brighter the surface of the object, the greater the amount of reflection.

Absorption of light by an object is also dependent upon its color, darker objects absorbing a greater amount of light. These dark objects not only absorb but radiate heat more rapidly.

Sunlight in its passage through the air loses energy. The amount of the loss is controlled by the position of the sun, the density of the air strata

and the amount of moisture and foreign matter in the air. The loss of energy is proportionate to the amount of refrangibility of the ray, the greatest loss occurring at the violet end of the spectrum and the smallest at the red. The percentage of ultraviolet and light rays is therefore greater at higher altitudes.

PENETRATION OF SUNLIGHT IN THE HUMAN BODY

That sunlight will penetrate the human body has been proved by Malgat, Finsen, Kime, and others. They were able to obtain impressions of objects on photographic plates by passing sunlight through the chest.

As to the penetration of the individual rays, Finsen states that the penetrating power of the different colors is inversely proportionate to their power of producing inflammation. Kaiser, by excluding all of the rays except the blue and the violet, obtained an impression upon a photographic plate through the chest. Busk was unable to obtain this result through his hand in ten minutes. Schmidt found that the penetration of the red rays through fatty tissue took place in one second, and through muscles in one minute. Lenkei, by the use of blue and yellow rays, was able to penetrate tissue a distance of one inch, but in the absence of muscle this was increased to three inches. The red rays, he found, were still more penetrating. Finsen found that the short length ultraviolet rays were absorbed by the epidermis and that the inner long-length ultraviolet, as well as the blue-violet, rays reach the capillary network of the blood. Here, according to Busk, 99 per cent are absorbed. Sanborn and Woodruff, from their experiences in the tropics, bear out the statements of Finsen and Busk, as to the penetrative power of the ultraviolet ray, by saying that this ray is absorbed by the pigment in the skin. Rollier and Mierowsky have advanced the theory that the ultraviolet rays, upon entrance to the pigmented skin, are changed from short to long wave-lengths, thus permitting greater penetration.

This theory has as yet not been proved; and it has been recently shown that fluorescence is less marked in pigmented skin than in unpigmented skin. In a more recent publication Rollier makes statements that would seem to indicate a change in his views. He says, "The experiments of Weissner, demonstrating the powerful bactericidal action of the infrared rays, show that it is not only the ultraviolet rays which are of therapeutic importance. On account of their greater wave-length and amplitude, the infrared rays give out a considerable amount of

heat when they impinge on the surface of the body, and in comparison with the superficial action of the ultraviolet rays they have quite remarkable powers of penetration." Duncan felt that heat insolation was due to the ultraviolet and light rays, but Woodruff observed that this condition occurs frequently in the dark races, who absorb light and heat more rapidly and in whom the greatest penetration is by the red and infra-red rays, which are richest in heat energy. This rapid absorption of heat by the dark races places them at a disadvantage when their environment is hotter than their body temperature; but by the law of radiation their pigmented skins aid them in radiating heat more rapidly when their environment is cooler than their body temperature. It is this failure to radiate heat by reason of lack of pigment that renders the white race so susceptible to insolation. Woodruff states, "As a rule, in races of men, the amount of pigment is sufficient to protect from the maximum amount of ultraviolet light to which he is exposed at any time in the year in the climate which evolved the type." In addition to this natural means of protection, we might mention that Sanborn advised the wearing of clothes made of red, orange or black cloth. Sorrentino, in the treatment of lupus, painted the surface of the lesion with an arsenate, thereby excluding the ultraviolet ray, and Becker and Brieger painted their casts black or covered them with black flannel. These measures were adopted to exclude the ultraviolet ray; but Sorrentino thought that his technique favored penetration of the other rays, and Becker and Brieger found that atrophy of the part encased in the black casts was less than in the usual white plaster of paris. May we not then assume that increased pigmentation is not merely a protective covering for the body against the irritating effects of the short wave ultraviolet, but also increases light penetration, heat absorption, heat production and heat radiation?

There are many unbelievers who refuse to be convinced that light does penetrate just as there are those who discredit heliotherapy. Criticism of the work done by such men as Finsen, Malgat,Kime, Lenkei, Kaiser and others has been persistently made, but in the main their work must be accepted. Experiments have been made under varying conditions. This is true not only of penetration, but of all experimental work that has been done on the action of light. When working conditions are uniform, unanimity of opinion among the various observers will result.

EXPERIMENTS ON THE PENETRATION OF SUNLIGHT

In June, 1921, Balderrey began a series of experiments to determine the effect of sunlight on the human body. His first work dealt with the penetration of light.

The object in view was to determine the amount of tissue through which light might pass and influence a photographic plate, and also the effect of pigmented skin in aiding or hindering its passage. Persons with and without pigmentation were used in our experiments. The question of body heat as a factor in producing impressions upon plates having been raised, to eliminate this possibility, pieces of beef of varying thicknesses were used. No differences in the results were noted. Moreover, the makers of the plates used have assured us that moderate degrees of heat will not affect them and that the only effect of heat which might occur would be softening of the gelatin to such an extent that it might run. This occurred in one instance, in an experiment upon a colored patient on an exceptionally warm day after a rather long exposure.

Three hundred and eight experiments were made on light penetration. They were made during the months of June, July, August and September, 1921, between the hours of 9.30 A.M. and 4.30 P.M. In the majority of instances the work was done between 11.30 A.M. and 2.30 P.M. when the sun's intensity was greatest. A few experiments were also made with an artificial source of light, the carbon arc with carbon electrodes and giving a light of 260 candle power.

The methods employed were as follows:

Subjects were taken to the dark room used by the X-ray department for developing purposes. Here they were prepared for the experiment either in subdued red light, faint green light or total darkness. These same light conditions were observed in handling the plates or films which were used. The plates or films were placed in ordinary negative holders. Using these in conjunction with the negative carrier, such as is employed in photography, it was possible to make many experiments by merely introducing the loaded negative holders into the negative carrier as needed, after the subject had been prepared for the exposures in the dark room.

In the preparation of the subject the following technique was carried out:

For example, in the experiments done on the penetration of light through the chest, the persons were stripped to the waist. The negative carrier was next fastened to the posterior surface of the body by means of wide strips of adhesive. Attached to the negative carrier was a large square of light-proof cloth. After the negative carrier had been placed, the light-proof

cloth was bandaged to the body, so that the entire upper portion was enclosed from the hips to the neck. On the anterior chest wall was an opening four inches square, through which light could fall upon the skin. The edges of the opening were securely strapped down by means of adhesive, so as to prevent the entrance of light except over the four-inch square. A second light-proof cloth excluded the light from the opening until the experiment was about to be made. It covered the negative carrier, and was so arranged posteriorly that holders could be placed in the negative carrier by the hand, working under the cloth. After the negative holder had been placed, the right hand was introduced under the cloth and the pressed board cut-off of the negative holder was pulled out, so that any light penetrating the chest would fall upon the plate; meanwhile, the left hand was holding the cloth tightly about the right forearm to prevent admission of light elsewhere. This would seem an unnecessary precaution, as the negative holders are so constructed that the pressed board cut-offs may be fully removed and reinserted into the holder in bright light with safety. The surface of the plates was two inches from the skin surface of the body. With this technique the amount of light falling upon the body and its point of entrance could be controlled, and the depths penetrated were definitely known.

We at first placed all objects to be photographed directly upon the plate, and reproductions of various articles and words describing the experiments were obtained. This method proved fairly simple; but we later attempted to reproduce upon plates images of articles placed in front of the tissue to be penetrated. We have found it extremely difficult to obtain as clear-cut impressions with the object between the tissue and the sun as was possible with the object between the tissue and plate; but reproductions are found, and the loss of sharp, definite outline of the object is due to scattered and refracted rays.

We were not always successful in obtaining impressions upon our plates, since the position of the sun, the part exposed and the plate apparently influenced our results. This was undoubtedly due to refraction and scattering of the rays. These failures to cause impressions on some of the plates are, perhaps, sufficient proof that impressions on the positive plates were not due to heat; as, frequently, when two persons were subjected to the sun at the same time we obtained impressions on one plate and not on the other. Impressions were made through the hand, forearm, knee, thigh and chest. The greatest depth penetrated was 10 inches. One hundred and ten experiments were made on depth penetration of light.

A study was next made of the influence of pigment upon penetration. In this work two types of subjects were used. Those skins classed as pigmented were in brunettes who had previously taken solar radiations and the deep chocolate-brown color characteristic of complete tanning in this type was present. The unpigmented subjects were blondes who had never had suncure and were not receiving this form of treatment. They gave a history of pigmenting slowing and poorly. In some, solar erythema and freckling occurred upon the portions of the body (face, neck and forearms) exposed to the sun's action during the summer months, evenly distributed pigmentation never occurring. The others tanned slightly during the summer. It was found that with pigmentation the plates were more quickly affected by the penetrating light and the intensity of the action was greater. Sixty-five observations were made. The pigmented and unpigmented subjects were prepared and the experiments made simultaneously, all conditions such as intensity of light, time of day, length of exposure and amount of light falling upon the place of entry being similar.

Another series of experiments was made to determine the penetration of the different rays of the spectrum. For this purpose Wratten light filters were used, as follows: no. 25, transmitting wave-lengths 580 to 700, total transmission 22 per cent; no. 58, transmitting wave-lengths 480 to 700, total transmission 23 per cent; no. 48-A, transmitting wave-lengths 400 to 510, total transmission 1 per cent.

By combining different filters it was possible to exclude all but single portions of the visible spectrum; but in so doing the total transmission was at times so much reduced that impressions upon the plates were obtained only through thin portions of tissue under the most favorable light conditions. But by using filters which transmitted the wave-lengths of several adjacent portions of the spectrum, results were obtained without difficulty. These experiments were also tried with both pigmented and unpigmented subjects. For comparison we subjected thin portions of the body such as the hand to long exposure under the Alpine sun lamp, but we were unable to obtain penetration.

In these experiments it was noted that the penetration of light was greatest as the red portion of the spectrum was approached. Progressing from the red to the blue, longer periods of exposure were necessary, and the intensity of the action upon the plates was markedly decreased. In this series it was again observed that pigmentation facilitated penetration.

By means of a Bausch & Lomb spectrum projector with carbon arc light, reproductions of the spectrum were made through thin portions of tissue, skin, muscle, fat, intestines and stomach. Fifty-one of these experiments were made. They proved most satisfactory in demonstrating the penetration of the different rays. Through very thin portions of tissue (0.4 mm.) the entire visible spectrum was reproduced upon plates with varying intensity of light action, decreasing as the refrangibility of the rays increased. The addition of more tissue gradually reduced the penetration of the different rays, until only the red produced action upon the plates.

The influence of concentration of sunlight upon penetration was determined by using the Thezac-Porsmeur lens. This is a lens used as an adjunct to heliotherapy by Pryor and LoGrasso in cases of stubborn infected sinuses and ulcers that have failed to respond to sun treatment. It is a biconvex lens, 12 inches in diameter and with a focus of 72 inches. It is so focused on the lesion that it forms a circle from 6 to 8 inches in diameter. It was used in this manner during the experiments.

Pigmentation again favored light penetration and, by concentrating the light, action on the plates was obtained in about one-half the time required without focalization. The light action upon the plates was extremely intense, being greater than that obtained in any other of the experiments. Twenty-five of these experiments were made.

Other experiments, based on the sensitivity of the eye to the various colors, were made. Through a small square opening in a light-proof cloth, portions of the body were exposed to the sunlight, and observations were made as to the colors seen when whole sunlight and red, yellow, green and blue rays fell upon the parts. The colors transmitted were noted by three observers, who were able to differentiate as to the intensity of light transmitted. It was not possible to specify the color of the filter which had been imposed upon the part. With whole sunlight an intense red color could be observed and this intensity was diminished by the use of either the red or yellow filters. With the green filter the amount of light transmitted was too small to be detected, while with the blue a slight purplish color could be seen with extremely bright sunlight. The greatest thickness penetrated was one and one-quarter inches.

From our experience we have concluded (1) that sunlight will penetrate the body to a depth of ten inches, (2) that the penetrative power of the individual rays increases as refrangibility decreases, (3) that concen-

tration of sunlight favors penetration and (4) that pigmentation is not merely a protective agent against the caustic action of the chemical rays of the spectrum, but an important factor in favoring the penetration of light, inasmuch as it changes a white reflecting surface to a dark, light-absorbing one.

THE PRODUCTION OF PIGMENTATION

To test the pigmenting properties of various portions of the spectrum the five different filters already described were used. These filters which were three inches square were placed upon the chest of subjects during their exposure to sunlight. It was found that pigmentation was most marked under the blue rays, slight under plain glass and green rays, and entirely absent under the red and amber filters.

While on the subject of pigmentation, it might be mentioned that it has been reported that a positive Pirquet reaction is not observed when the test is applied to pigmented skin. In our experience this was not found to be true. It was tested by keeping one arm of a patient covered during the radiation period, so that pigmentation was prevented. Later, when pigmentation of the remainder of the body was effected, Pirquet tests were made on both arms. No change in the intensity of the reaction was observed.

THE EFFECTS OF DIFFERENT WAVE-LENGTHS UPON THE GROWTH OF ANIMALS

The influence of different portions of the spectrum upon the growth and development of animals was observed, young guinea pigs being used for the purpose. They were placed in well ventilated boxes, 14 x 14 x 42 inches, each box accommodating three animals. The only light entering was through filters which transmitted different parts of the spectrum. The red filter transmitted wave-lengths 580 to 700, total transmission 22 per cent; the green, wave-lengths 510 to 700, total transmission 23 per cent; and the amber, wave-lengths 510 to 700. As these experiments have been conducted throughout the winter months, when the sun's light would not be constantly available, the animals have been exposed to the light of the carbon arc with pure carbon electrodes. Their exposures have averaged three hours a day. In the first series an additional group of animals was placed under blue light, wave-lengths 360 to 500; but as the total transmission of filter was only 0.6 per cent its use was dis-

continued. The animals in the first series were under these filters 70 days. The average gains in weight were as follows; amber filter, 241 gm.; blue filter, 201 gm.; red filter, 106 gm.; green filter, 34 gm. In the second series the animals were observed for 78 days with the following average gains in weight: red filter, 369 gm.; plain glass (controls), 321 gm.; green filter, 265 gm.; amber filter, 240 gm.

A fourth series gained as follows: red rays, 609 gm.; X-rays, 592 gm.; ultraviolet rays, 496 gm.; controls, 462 gm.; green rays, 287 gm.; and amber rays, 273 gm. The animals receiving X-rays were treated at three-week intervals with 8 in. of spark gap; 4 *m.a.*, 8 in. skin distance for 4 minutes. Those under ultraviolet rays received 30 minutes' exposure under the Alpine sun lamp (Hanovia) each day. All animals were under observation for 114 days.

A third series on the sixtieth day had made the following average gains in weight: red filter, 275 gm.; amber filter, 264 gm.; plain glass (controls), 262 gm., and green filter, 145 gm.

An interesting fact was noted in the third series. One of the three animals under the red filter developed normally up to the fourth week, when the weight for a time remained stationary. During the next four weeks persistent loss of weight was noted. At the end of the 61 days the animal died, and at postmortem showed three large tuberculous ulcers of the intestine. The other two animals continued to gain in weight and at the present time are apparently healthy. This seems remarkable when one considers that they were constantly subjected to the infectious excreta of the diseased guinea pig.

These experiments were begun late in summer of 1922, and it was planned to use the sun's energy and expose the animals for three hours each day, dividing this into one and one-half hour periods, morning and afternoon, corresponding to the hours of suncure for patients. To our great surprise, the guinea pigs under the green filter died of heat insolation after about one and one-half hours' exposure. This occurred in every instance. More work was done along the lines of the immediate effects of light by using the carbon arc lamp. Animals were exposed to the action of a single lamp of 260 candle power. During exposure of three hours' duration we noted that all the animals showed symptons of heat insolation. These signs were evident at the end of one hour and fifteen minutes and were most marked in animals under the green filter. Cutting off the infrared rays by means of distilled water, alleviated the symptoms. The animals at once became quieter, and respirations and temperatures

decreased. In this connection it was observed that, when the infrared rays were cut off from only one-half of the filter, the animal placed its head under this portion. The body might or might not be exposed to the light containing infrareds, but the head never. The average losses in weight under these filters, following three-hour exposures were: green, 35 gm.; amber, 30 gm.; red 27 gm.; blue, 16 gm.

Rabbits exposed to direct sunlight, under filters, died in the following order: amber, and then red. Those under the green filters were alive at the end of three hours. These differences in results in the two types of animals may possibly be due to the difference in species. To say that heat insolation is the cause of death may be correct; but, when one considers the predominant properties of the spectrum to which these animals were exposed and that deaths were under the filters which transmitted less of the red or heat portion, it is perhaps best to look for some contributing cause. Persistent failure of those animals receiving only light from the middle of the spectrum to gain weight like those under other wave-lengths is also very suggestive. Three important questions may be asked. Is the middle portion of the spectrum of any therapeutic value? Is it injurious because it emanates more energy? Are the curative rays those at the extremes of the visible spectrum, in conjunction with the adjoining rays of the invisible spectrum? We would hesitate to offer any explanation of the results, but more work is being done in this direction and will be reported later.

CARBON ARC LIGHT THERAPY

The ideal conditions, under which heliotherapy might be conducted at maximum efficiency, would require sunlight during each day of the year and the same degree of intensity of the sun's energy for each day. Unfortunately the sun's energy is not always available for therapeutic purposes. Daily variations in the condition of the weather and seasonal changes with their varied intensity of sunlight leave much to be desired. Especially in the Great Lakes region, where we are situated, do these factors materially influence the giving of the required amount of solar radiation to effect a cure in the shortest possible time. Continuous and steady improvement, such as may be noted under ideal conditions during the summer months, is impossible, and hence the period of treatment is prolonged. To maintain a more persistent improvement and shorten the length of treatment, various artificial sources of light

energy have been used. The two that have been most commonly employed are the Alpine sun lamp and the electric arc mentioned above. During the past seven years the Alpine sun lamp has been used in the J. N. Adam Memorial Hospital when weather conditions or seasons interfered with the use of the sun's energy. During the winter of 1921-1922 the electric arc with electrodes of carbon has been used as the source of radiant energy in the treatment of a series of cases.

The electric arc was selected because its spectrum resembles very closely that of sunlight. Carbon electrodes were used, as the light from them is less rich in the short light frequencies or ultraviolet rays than the iron and carbon arc or iron arc.

Therapeutically, the electric arc corresponds very favorably with sunlight. It has been found of value in the treatment of tuberculosis, and has been used by Reyn and Ernst, Finsen, Cleaves, Freund, Freudenthal, Kaiser and Tsiechawski. It has also proved beneficial in many nontuberculous conditions, as in diseases of the skin, infected wounds and, more recently, rachitis. Unger and Hess in their work have attempted to show, by means of radiographs, changes in the bones following its use in rachitic children. Reyn and Ernst used both the carbon arc and mercury vapor quartz lamp, but found their results better with the former. Pigmentation of their patients occurred. Kime treated pulmonary tuberculosis with the carbon arc with good results, his only mistake being to attribute his results to the ultraviolet rays alone. Tsiechawski made use of the light in treating tuberculous joints, using light equal to 12,000 candle power with excellent results. The length of time patients were exposed to the light at each treatment varied from ten minutes to one hour each day.

The experience of Finsen, Rollier, and Pryor and LoGrasso causes them to state that there is no adequate substitute for sunlight and that the sun's energy combined with altitude is the method of choice. We must at this time accept natural sunlight as the best form of radiant energy available for the treatment of disease. In accepting this we should realize that not only the ultraviolet energy but all the radiant energies of the sun are necessary for hygiene and santitation, prevention of disease and curative action. The quality and proportion of the rays as found in natural sunlight are ideal, and in selecting a substitute to be used, when the sun's energy is not available, we should try to counterfeit natural sunlight as closely as possible. As Dorno has said, "It shows our ignorance of the action of light on the human body that we believe we can produce the

same effects with the quartz-lamp treatment as with sunlight." Before giving to the ultraviolet rays full credit for those cures obtained in heliotherapy, it is well to recall that patients are not exposed to solar radiations during the hours when these rays are most plentiful; that the percentage of these, even in high altitudes, is small when compared with the other rays found in sunlight; and that never do they approach the number given off by the Alpine sun lamp. The results obtained by the use of the Thezac-Porsmeur lens cannot be attributed to the ultraviolet rays, as they are filtered out by the glass. It must be borne in mind that other parts of the spectrum are also chemically active, being identical except in rates per second and distances apart. Rieder, Gerhartz, Nagelschmidt, Artault, Becker and Brieger were exponents of the effectiveness of long wave-length rays, using in their work the red heat rays.

The spectrum of the electric arc shows an excess of orange and green rays and a slight deficiency of the blue, the ultrared and ultraviolet rays being greatly increased. The luminous efficiency of the arc is as high as that of any artificial light; that is, 13⅓ per cent. Taking the intensity of red as a unit, the composition of direct sunlight and of the carbon arc was found by Abney to be:

	SUNLIGHT	CARBON ARC
Red	100	100
Green	193	203
Violet	228	250

In the treatment of our cases the type of lamp chosen was the one used so commonly a few years ago in the lighting of streets. The spherical candle power of each lamp was 260, and with four arcs in the room we obtained 1,040 candle power. Solid carbon electrodes were used, as by this means we could more closely approach sunlight. Four of these lights were placed in a room, one in each corner at a height of 66 inches. In the other room three lights were hung in the centre of the room, 70 inches from the floor. The rooms in which the treatments were given were 9 x 9 x 10 ft. Walls and ceiling were enamelled in white, so as to giv a good reflecting surface. The floor of each room was covered with white canvas that could, from time to time, be removed and cleaned.

On the adult ward bed-patients were taken into the rooms in their beds, two cases receiving treatment at once. In the children's ward we were able to treat as many as five at one time. These cases were all

treated while fully undressed, except for breechclout, and in the prone position.

On January 10, 1922, treatment of a series of 15 cases was begun. Preceding the treatment the following observations were made: photograph, radiograph, measurements of the diseased part, blood examination including estimation of hemoglobin, number of red and white cells and differential blood count, urinalysis including specific gravity, albumen, sugar, total solids and bacteria, weight of discharge from sinuses if present, weight of patient, temperature, weight and examination of sputum, pulse and respiration. Records were also made of temperature of patients before and after treatment, temperature in sinus, if any, and a count of the pulse and respiration during the time of treatment, and temperature of the room at the end of the first half of the treatment period and on its completion.

On the first day patients were given a total exposure of 16 minutes, divided into four single exposures of four minutes each, two minutes anterior and two posterior. The total length of the exposure was increased at the rate of 16 minutes per day until on the sixth day the total was one hour and thirty-six minutes. Upon the seventh day the time was doubled, so that our cases received three hours of treatment per day, one and one-half hours morning and afternoon. No ill effects from the condition of the air of the room were noted, and even at the end of an hour and a half period of treatment there was no appreciable change in the room temperature.

In the selection of our cases we wished to treat only those patients who had recently been admitted to the hospital. Twelve of these patients were new arrivals and had not had any suncure. The other three cases had been in the hospital over various periods of time and had had previous treatment by exposure to the sun.

The results noted in those cases that received over three months' treatment may be summarized as follows:

	per cent
Hemoglobin, increased	67
Erythrocytes, increased	50
Leucocytes, decreased	17
Lymphocytes, increased	50
Temperature, return to normal	100
Weight, gain	85
General condition, improved	85
Surgical lesion, improved	85
Wound discharge, less	100
Sputum, reduced	100
Sensitive to light	20

The following shows a comparison of these cases with others under treatment by suncure or the usual rest cure:

	IMPROVED	HEMOGLOBIN INCREASED	LYMPHOCYTES INCREASED
	per cent	*per cent*	*per cent*
Carbon arc. Lymph node, bone and peritoneum..	83.30	83.30	66.64
Sun cure. Pulmonary.....	89.50	89.42	89.42
Rest cure. Pulmonary.....	77.77	55.55	77.77

These results warrant further use of this artificial source of light energy. It can in no way be compared to the sun's energy, but by employing it during the winter months we may maintain more firmly the improvement obtained by solar radiations. If it will do this, much has been gained.

Perhaps one of the reasons why it has not proved more efficient is the fact that the conditions under which it has been applied have been much less favorable than those prevailing with suncure, one of the most notable disadvantages being the lack of fresh moving air. If suncure conditions could be duplicated, it is reasonable to suppose that pigmentation with the carbon arc might be much more marked and the results obtained more definite. Towards this we are striving and the results of further work in this field will be reported.

BLUE LIGHT THERAPY

Wave-Length 360 to 500

Two conditions, namely acne and scars, have been treated by means of this light. The carbon arc light with carbon electrodes was used as the source of light. Blue filters, transmitting wave-lengths 360 to 500, were placed at a distance of 12 inches from the lamp. The patients exposed the affected areas to the light transmitted through the filter. Treatments were begun with exposures of 10 minutes. These exposures were increased by 10 minutes each day to periods of one hour. Very severe acnes of the face which had failed to respond to other therapeutic measures benefited greatly by this treatment. At the end of two weeks marked improvement was found. The lesions were drier and less numerous, and a marked decrease in the occurrence of new ones was noted. This improvement continued until at the end of six or eight weeks cure was effected or marked beneficial results occurred. Ten patients with acne have been treated with very good results in all instances.

Unfortunately, all patients who were treated for scars had had this condition existing for over a year. These old vivid and disfiguring scars were, however, greatly improved. The red inflammatory appearance disappeared, and bleaching took place. There was also apparent smoothing of the surface.

During these treatments of both conditions, when the patient had dark or light brown hair definite bleaching took place. This bleaching effect was also very noticeable in the old scars of the acne patients.

CONCLUSIONS

1. Sunlight will penetrate the human body to a depth of ten inches.
2. The penetrative power of the individual rays increases as the refrangibility of the ray decreases.
3. Concentration of light by means of a biconvex lens (Thezac-Porsmeur) favors penetration.
4. Pigmentation is not merely a protective measure against the caustic action of the highly chemical short wave-length rays of the spectrum, but is also an important factor in favoring the penetration of light, inasmuch as it changes a white reflecting surface to a dark light-absorbing one. This is of great importance, for it is in part the equivalent of increasing the intensity of the sunlight striking the surface of the body. It is also probable that the body with its darker surface radiates heat at a slightly increased rate, thus permitting the subjection of the body to longer periods of radiation without the production of symptoms of insolation.
5. Pigmentation is produced by the wave-lengths shorter than 480, increasing as the wave-lengths become shorter and more refrangible.
6. The wave-lengths at the extremes of the visible spectrum are more stimulating to the growth and development of guinea pigs than those of the middle portion.
7. Severe acnes respond to treatment with blue light, wave-lengths 360 to 500, when other measures have failed to effect a cure. This part of the spectrum is also of great value in bleaching and smoothing vivid and disfiguring scars.

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Penetration of light through cheek, three-eighths inch of tissue

	AVERAGE TIME	SOURCE OF LIGHT	CONCENTRATION OF LIGHT	RED WAVE-LENGTH 680–700, T.T. 22 PER CENT	GREEN 480–610, T.T. 23 PER CENT	BLUE 400–490, T.T. 0.1	ACTION ON PLATE
	seconds						
Pigmented	1	Sun	+				+++
Unpigmented	1	Sun	+				+++
Pigmented	1	Sun		+			+++
Unpigmented	1	Sun		+			+++
Pigmented	3	Sun			+		++
Unpigmented	3	Sun			+		++
Pigmented	15	Sun				+	+
Unpigmented	15	Sun				+	+

Penetration of light through forearm, three and a half inches of tissue

	AVERAGE TIME	SOURCE OF LIGHT	CONCENTRATION OF LIGHT	RED	GREEN	BLUE	ACTION ON PLATE
	minutes						
Pigmented	5	Sun	+				+++
Unpigmented	5	Sun	+				++
Pigmented	3	Sun		+			+++
Unpigmented	5	Sun		+			++
Pigmented	5	Sun			+		+
Unpigmented	5	Sun			+		+
Pigmented	7	Sun				+	+
Unpigmented	7	Sun				+	+

Penetration of light through abdomen, seven inches of tissue

	AVERAGE TIME	SUN	LENS	ACTION ON PLATES
Pigmented	2 minutes	+	+	++
Unpigmented	1 minute, 10 seconds	+	+	+++

Penetration of light through chest, ten inches of tissue

	AVERAGE TIME	SOURCE OF LIGHT	CONCENTRATION OF LIGHT	RED	GREEN	BLUE	ACTION OF LIGHT
	minutes						
Pigmented	10	Sun					+++
Unpigmented	10	Sun					++
Pigmented	3	Sun	+				+++
Unpigmented	3	Sun	+				++
Pigmented	15	Sun		+			+++
Unpigmented		Sun		+			++
Pigmented	15	Sun			+		+
Pigmented	15	Sun				+	+

SURGICAL INTERVENTION IN PULMONARY TUBERCULOSIS[1, 2]

PATHOLOGICAL CONDITIONS IN THE LUNG AND THE VARIOUS FORMS OF OPERATION APPLICABLE TO THEM

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The healing of certain forms of pulmonary tuberculosis, some of them comparatively benign and of slow progress, is stopped, not so much by lack of bodily resistance as by mechanical conditions prevailing in certain diseased chests.

Among these forms are those with large upper lobe cavities, which, as far as we can gather, rarely if ever heal, but whose bearers carry them until secondary infection, chronic sepsis and amyloid degeneration, or, finally, for unknown reasons, a progression of the pulmonary tuberculosis itself or a miliary dissemination brings a long period of invalidism to an end. Still other forms, in themselves benign, are those tending to extensive sclerosis and shrinkage, in which the disease itself or the carrier has the property of throwing out fibrous tissue around the foci of tuberculosis, and in which neither the extent of the infection nor the lack of resistance, but rather the mechanical limitations set by the bony framework of the thorax, prevent a final cure. Yet others are sclerosing phthises that actually have been cured, so far as tuberculous activity is concerned, but which through the very process of cure have had their viscera so distorted, and their tracheas so bent and pressed upon by neighboring blood vessels and other unyielding attachments, that the effects of the natural cure, the wheezing, the dyspnea, and sometimes the cyanosis, are quite as distressing, if not as dangerous, as were the symptoms of the foregoing tuberculous disease.

Finally, there are cavities near the hilum that are dangerous and difficult to heal: dangerous because they lie closer to large blood vessels than more peripheral cavities and are more prone to profuse hemorrhage

[1] From the Division of Surgery, Medical Department, Stanford University.

[2] Presented at the annual meeting of the National Tuberculosis Association, June, 1923, Santa Barbara, California.

from them, difficult because the lung is less yielding at the centre than at the periphery, being threaded and sustained by a system of cartilaginous tubes, stiffest at the centre.

These pathological manifestations, then, the very large upper lobe cavities, the very extensive sclerosing phthises, and the hilum cavities, are rarely cured naturally or by medical means. The bony framework of the thorax has set a limit to the possibility of their obliteration; and where this limit has been overcome the shrinkage is so vast and so distorting to the unaffected thoracic viscera, which have to make up for it, that the cure is almost as distressing as the disease. In many of these manifestations it is not so much the tuberculosis that needs cure as it it the end results of the disease and the deformities occasioned by them.

Many of these forms of tuberculosis and the anatomic distortion arising from them can be helped by artificial pneumothorax. In many of them, however, and this in the most chronic and benign forms, the accompanying obliterative pleurisy makes pneumothorax impossible; in others, adhesions hold the cavity open in spite of the collapse of other parts of the lung.

Fortunately, mechanical means other than pneumothorax can accomplish the same result and, if necessary, perfect an incomplete one. When a pneumothorax is impossible thoracoplasty can collapse the chest; when it is incomplete we can sever adhesions with the knife or the cautery; or, in tuberculosis affecting the lower part of the lung, we can paralyze the diaphragm, cause it to rise and set the lower part of the lung at comparative rest, by extracting the phrenic nerve.

It is unnecessary at a meeting of this kind to review again the history of surgical intervention in pulmonary tuberculosis, to speak again of the efforts of the ancients, of MacEwen's celebrated lungless carpenter, of Forlanini, and of the modern developments, of the work of Brauer and Friedrich, of Sauerbruch, and of Archibald. It is unnecessary to emphasize the dangers, perhaps, of open discussion. For there are dangers that every one who has occupied himself with this kind of surgery has felt; dangers that pulmonary tuberculosis might be recognized as a surgical stamping-ground. The promiscuous invasion of sanatoria by surgeons is something that one scents not too far off and recoils from with a shudder.

We should like, therefore, to recount some of our difficulties and ask your advice; to relate some interesting physiological observations and discuss some of the results, which, we confess hesitatingly, have been satisfactory so far.

Ordinarily, surgical intervention finds its main indication in the impossibility of inducing a pneumothorax. Among the earliest endeavors was intrapleural pneumolysis—the severing and tearing of pleural adhesions in an attempt to collapse the lung. So sudden and rough an attempt at forcible collapse of the entire tuberculous lung was doomed to failure. This procedure was soon forsaken. Jacobaeus has come back to the same idea with his thoracoscope, an electrically lighted instrument, like a cystoscope, which he introduces through a small hole in the chest wall and with which he burns off adhesive strands in partial artificial pneumothoraces. It is impossible to see how this procedure can be other than imperfectly controllable. It has for its object the release of adhesions by which cavities in the lung are held open. Four patients, whose chests were opened with the same end in view, have taught us how risky the procedure is, and how impossible through a minute keyhole opening. These risks no one has better recognized than Jacobaeus himself: where the thoracoscope has revealed broad and firm adhesions he has abandoned attempts to sever them with his instrument.

These four patients, three of Dr. Philip King Brown's, and one of Dr. Mary Mentzer's had had pneumothorax performed. Their cavities, however, remained open, fixed apparently by strand-like adhesions between the chest wall and the lung. After much discussion and hesitation, a thoracotomy was done on the first patient. The question of anesthesia was the most difficult. Differential pressure was out of the question. Suddenly to balloon out the lung, which had been painstakingly collapsed by a long series of pneumothoraces, would surely have been disastrous. Graham's observations on open pneumothorax led us to try to open the chest under local anesthesia without the aid of steadying pressure devices. A large anterior trapdoor, made by sectioning the first, second and third ribs next to the sternum, gave good access: it was the greatest satisfaction, after throwing this trapdoor open and incising the pleura, to find that the patient continued to breathe exactly as before. This first patient was a woman of about fifty years, with tuberculosis of many years' standing. Her pleura was thick and her mediastinum apparently rigid. This gave us courage to open the chest. The other patients were younger women, whose mediastina were not so thick; they suffered no more respiratory difficulty than did the older woman.

This method of opening the chest under local anesthesia preceded by induction of a pneumothorax, seems to be of considerable promise. It

has proved itself able to supplant differential pressure apparatus in certain instances. It makes possible some operations that one would not dare undertake without it. We said that none of these patients suffered from air hunger, in spite of an opening in the chest many square inches in area, sufficient to admit the hand. This is not quite true. One did have a passing attack of respiratory embarrassment, the origin of which was interesting and curious to see. She was a little girl of fifteen. During the operation she began to cough, and, becoming frightened, strained. Immediately the lung, which lay collapsed at the bottom of the chest, ballooned out and began to flutter back and forth. I held the opening in the chest closed with a wet towel and quieted the girl. A few quiet breaths sufficed to reëstablish respiratory equilibrium, and the operation proceeded without further ado.

The adhesions in these four chests were of three kinds. There were, first, round strands corresponding to those seen in the X-ray, soft, an eighth of an inch or a little more in diameter, containing fairly large blood vessels and also some pulmonary parenchyma, drawn out into a long teat, and running almost if not quite all the way through the strand, a distance of several inches. These strands required ligation. They bled profusely when severed. The thermocautery alone was insufficient to staunch the bleeding from them.

Second, there were broad sheets and bands connecting the lung with the chest wall. These lay mostly at the top, and corresponded to a prolongation of the septum between upper and middle lobes. They were evidently the attachments of an interlobar pleurisy.

And, finally, there were broad and very firm adhesions connecting the apices to the chest wall, such as one finds at autopsy. It was impossible to separate these with the cautery. The lung was torn from the parietal pleura with the hand or, when the adhesions were firm, the parietal pleura, together with the lung, was separated from the chest-wall with the knife. This manoeuvre was painful, but it lasted but a few seconds. It would have been manifestly impossible to sever either the broad bands or these flat adhesions with the Jacobaeus instrument.

Of these four patients two have done well, two have not. In the two that did badly a fine catheter was left in the chest and air insufflated through it in the days following operation, so as to maintain the collapse. The insertion of the catheter was a mistake. In one patient the previous pneumothorax was lost; we were unable to introduce air into the chest; the lung has expanded, and we think that a thoracoplasty may be necessary. Another patient has an empyema, which had to be drained.

The value of this intrapleural pneumolysis is doubtful. It is a dangerous procedure; there is danger of breaking into a cavity or of having it break through into the chest by itself; the adhesions bleed readily. There is doubt, also, as to the indications; one may ask whether we have not let ourselves be guided too much by the X-ray and whether we have not been treating X-ray films instead of patients.

The typical Sauerbruch operation has been done ten times. There have been no fatalities. Three of the patients have been completely cured; that is to say, they are free from sputum or, if they do cough, their sputum has been free from tubercle bacilli on repeated examination. They have gone back to their previous occupations. Four are not cured but have been greatly improved. In two the operation is too recent to judge. In one the progression of the disease has remained uninfluenced. The fact that none of these ten patients with advanced and intractable tuberculosis has died in the three years now intervening since the first operation is fairly good evidence of its value.

The most difficult to cure have been those patients with large apical cavities and communicating pyopneumothorax. One of them has been operated upon twice; the remaining two will probably have to be. In the first one an extensive thoracoplasty with resection of long pieces of rib formed the first step. At the second a piece of clavicle and practically all that remained of the three upper ribs was removed without accomplishing an apical collapse. In communicating pyopneumothorax both sound and affected parenchyma have lost all power of expansion. The lung remains shriveled at the back of the chest. An extensive pushing in of the chest wall will probably be necessary, after the manner of Archibald perhaps, with the use of the pectoral muscle as a tampon.

In two patients the phrenic nerve was extracted, in order to paralyze one side of the diaphragm and raise its level. We approached the operation with considerable mistrust. The diaphragm has little to do with respiratory capacity. Expansion of the thorax unfolds the lung; the rise and fall of the diaphragm influence it but very little. I had occasion to measure this in a robust stevedore with a broken neck and a total paralysis from the lower cervical segments down. His breathing was entirely diaphragmatic. He was cyanosed and dyspneic. His capacity measured 420 cc. with the tank spirometer, or less than one-sixth of what it should have measured.

The operation, however, is simple, and may be of use in putting the lower parts of the lung at comparative rest in patients whose affection

lies at the level of the hilum or below it, especially those with central cavities. According to Dr. Helsley, recently from Sauerbruch's clinic, Sauerbruch uses phrenic extraction in patients of whose better lung he is in doubt. He does this small operation first. If the better side shows no signs of incompetency or exacerbation he does thoracoplasty later. If the better side shows a tendency to aggravation after the diaphragm of the other side has been paralyzed, he does nothing further. One of our operations has been done from this indication; the other for another reason. Dr. Pierson asked me to see a patient with multiple cavities and continued hemorrhages, up to three or four ounces a day, uncontrolled by posture, sandbags, drugs and all other standard forms of treatment. Pneumothorax had been tried, but was impossible. The man was very ill, he was bled white, he had several ounces of sputum a day and fever every evening. He had lost a great deal of weight. Without moving the patient from his bed, and under a local anesthetic, about 10 inches of the phrenic nerve was extracted. The man stopped bleeding, his temperature went down. Sixteen days after operation, just as he had begun somewhat to recover his strength, he began to bleed again. After he had had a profuse hemorrhage we proceeded to thoracoplasty as a desperate chance. The eleventh to the second ribs were resected under local anesthesia. The shock was unusually severe. The patient received a transfusion of 800 cc. of blood immediately after operation. He overcame his collapse in about two days. He has bled no more, he has stopped spitting, he has had no fever since operation, he has gained weight and bids fair to get well.

Goetze, Fischer and others have made extensive use of phrenic resection, both as an independent measure (in which Fischer reports almost 50 per cent of favorable results) and to complete the effects of partial artificial pneumothorax, especially that in which the lung is held distended and kept moving by basal diaphragmatic adhesions. Goetze goes so far as to recommend section of the phrenic in almost every case of artificial pneumothorax. I have no experience with the operation done on this indication.

Simple section or resection of the phrenic nerve in the neck is not sufficient entirely to stop diaphragmatic movement. Recent anatomic studies of Felix in Munich have shown that the phrenic may receive accessory innervation from the fifth spinal segment and that it has anastomoses further along its course, which may suffice to preserve some diaphragmatic motility after simple section or even resection of a

piece of the nerve in the neck. When the nerve is extracted slowly its accessory branches and anastomoses are pulled out with it. This extraction is not difficult; pieces ten inches in length may be removed by first cutting the nerve through and then slowly rolling its peripheral portion up on a hemostat, thus doing an exairesis after the manner first proposed by Thiersch for the extraction of trigeminal branches in facial neuralgia.

SUMMARY

1. Cavities which persist after pneumothorax, because of unyielding strands or adhesions may be collapsed by the intrapleural severing of these adhesions. The value of this intrapleural pneumolysis is not yet established.

2. When pneumothorax is indicated but not possible the lung may be collapsed by thoracoplasty.

3. Paralysis of the diaphragm by extraction of the phrenic nerve may be practised:

a. in order to set the affected lung partially at rest,

b. in order to determine the strain put upon the sound lung by partial inactivity of the affected side (as a test for future thoracoplasty), and

c. to complete the effect of an artificial pneumothorax when the lung is distended and kept mobile by diaphragmatic adhesions.

We should like to thank Dr. W. R. P. Clark for many kindnesses extended while these patients were in his wards at the San Francisco Hospital.

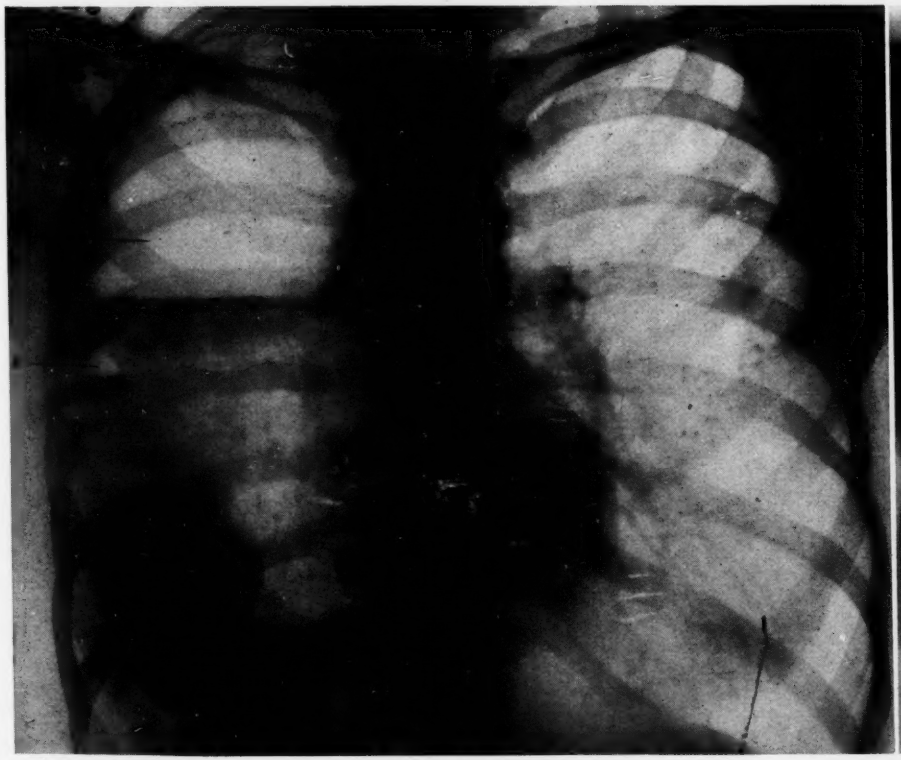

FIG. 1. VAST CAVITY IN UPPER RIGHT, WITH SECOND FLUID LEVEL (PYOPNEUMOTHORAX) UNDER IT

A: Cavity; *B:* Pyopneumothorax

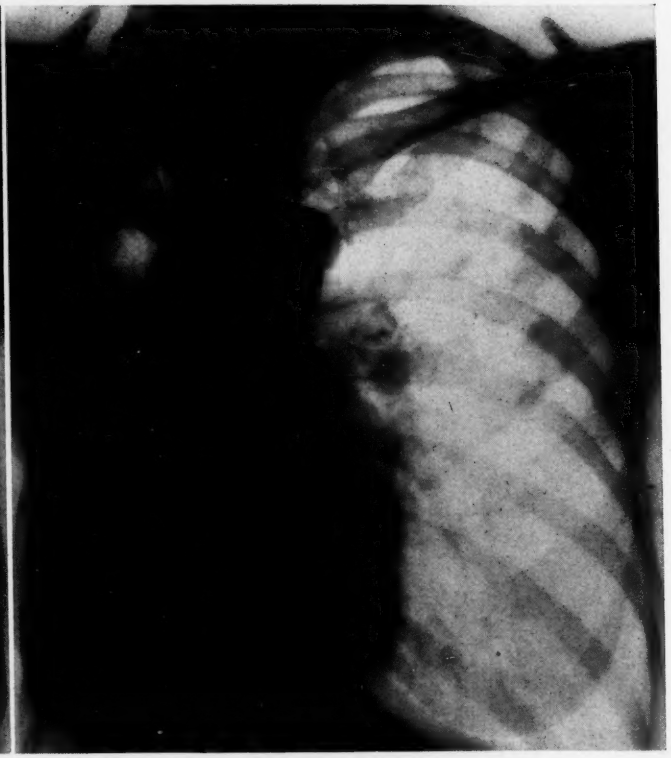

FIG. 2. AFTER COLLAPSE

Cavity smaller. Pyopneumothorax has disappeared. Heart retracted to right. Compensatory emphysema left lung.

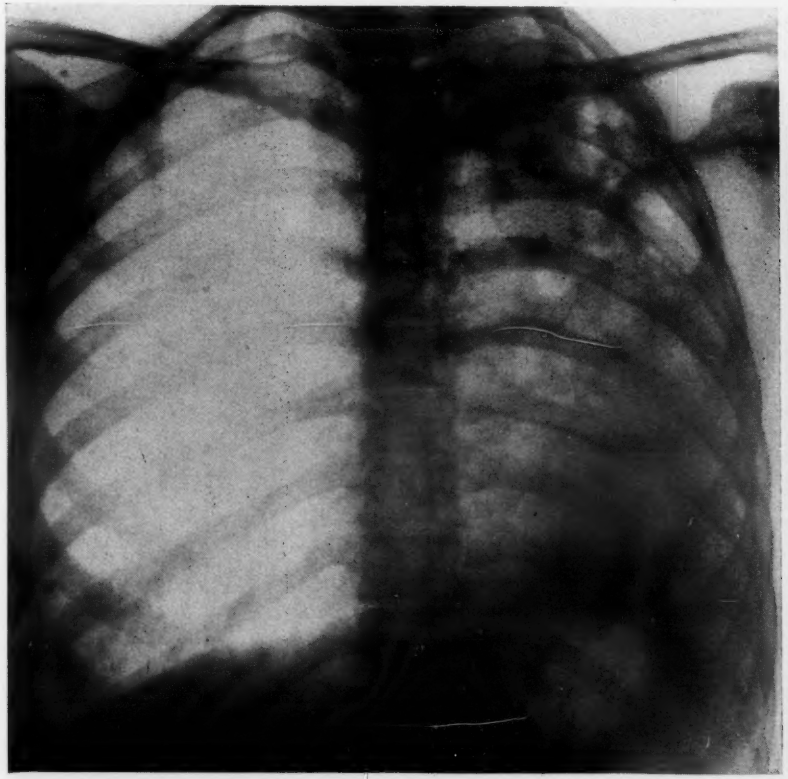

FIG. 3. SCLEROSING PHTHISIS IN LEFT LUNG. LARGE MULTIPLE CAVITIES IN UPPER LEFT. EXTREME DEVIATION AND KINKING OF TRACHEA

FIG. 4. AFTER COLLAPSE

Cavities closed. Trachea in midline and no longer kinked

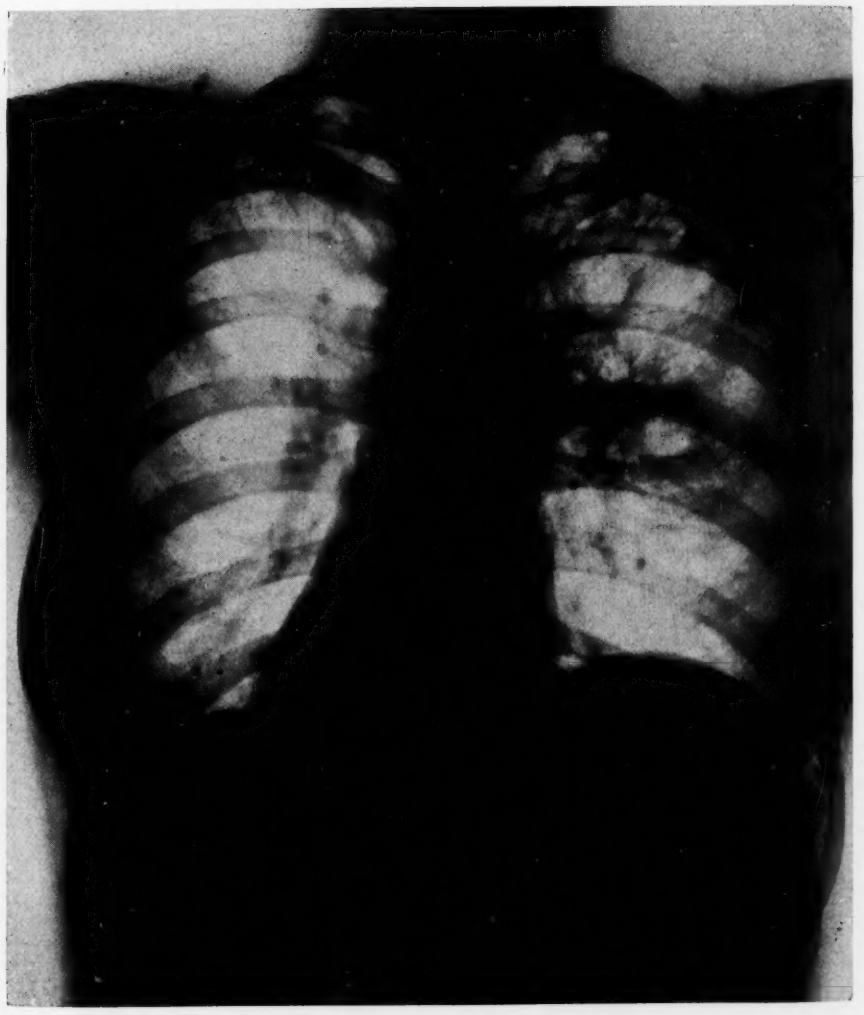

FIG. 5. MULTIPLE HILUM CAVITIES WITH FLUID LEVEL IN LOWEST ONE

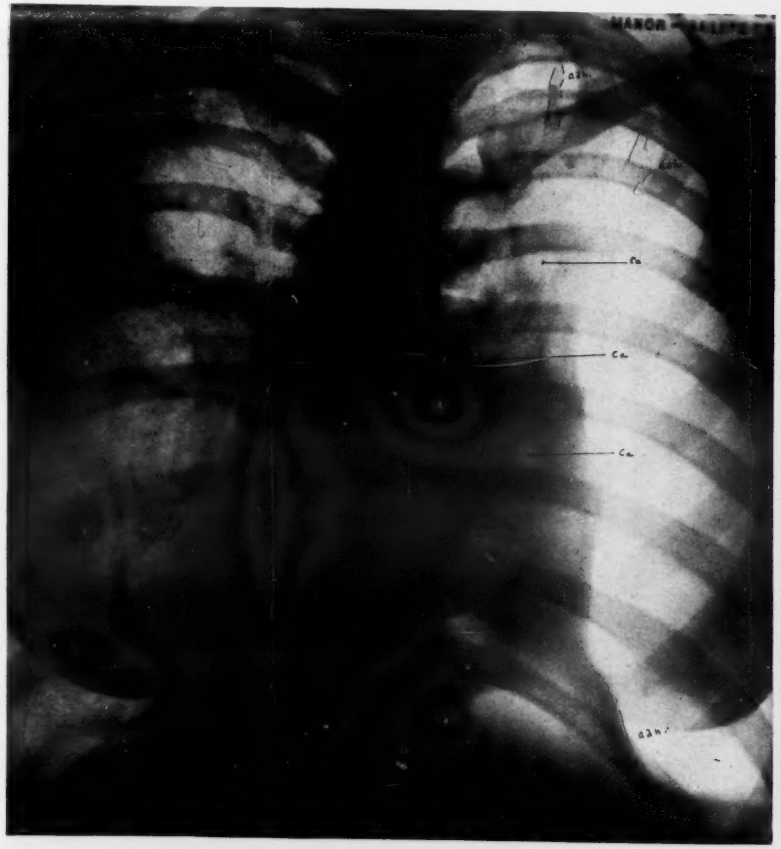

FIG. 6. AFTER PNEUMOTHORAX

Cavities persist in the collapsed lung, which is held distended by diaphragmatic and also by broad apical adhesions.

FIG. 7. AFTER SEVERING ADHESIONS AT OPEN OPERATION (INTRAPLEURAL PNEUMOLYSIS)

Cavities collapsed

THE EFFECT OF CARBON ON THE TUBERCLE BACILLUS IN VITRO AND ON EXPERIMENTAL TUBERCULOSIS IN THE RABBIT[1]

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The idea that the anthracosis of coal miners is antagonistic to the development of pulmonary tuberculosis is borne out by numerous statistical studies based upon postmortem as well as clinical findings. There have been numerous explanations of this effect, but these have been hardly more than suggestions and have lacked the stamp of accurate scientific analysis. Most previous investigations have also concerned themselves more with pneumonokoniosis as a whole, instead of taking the individual factors concerned and submitting them to test. In dealing with pneumonokoniosis the analysis has not been simple; yet in anthracosis, *per se*, the outstanding factor seems to be the carbon, which obviously can be submitted to test in fairly pure and individual form. Excellent reviews of the subject of pneumonokoniosis are presented in recent papers by Willis (1) and Gardner (2), in which the idea is expressed that the pulmonary lymphatic system plays a determining rôle in the development of lung tuberculosis. They presented reasons for supposing that dust inhaled into the lungs will so modify the pulmonary lymphatic anatomy as to produce a telling influence on the localization and progression of tubercle in the lungs of animals infected subsequent to dusting. The work demonstrated that dust particles, breathed into the lungs of animals under the natural conditions of cage life, find their way into the lymphatics and lymphoid tissue of the lung, where they in all probability incite anatomic (proliferative) reaction.

The theories of the actual mechanism of the injurious effects of inhaled dusts resolve themselves into three main groups, all observers agreeing that practically all dusts are injurious when inhaled over a long period of time: (1) those who believe the injury to be due to mechanical irritation with resultant connective tissue proliferation (Watkins-Pitchford);

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(2) those who believe the effect due to mechanical blocking of the lymphatics which normally provide a means of exit from the lungs (Krause); and (3) those who believe that the noxious properties are due to inherent characteristics which cause them to remain in the lungs for long periods (Haldane), such as insolubility, hardness, angularity, phagocyte-stimulating property, etc.

That the type of dust inhaled has something to do with the reaction to tuberculosis cannot be doubted in view of the findings reported from pathological and purely experimental studies on pneumonokoniosis. Silica is supposed to be the most dangerous of inhaled dusts, while coal dusts are least so. This was brought out especially by Mavrogordato (3) in 1918. He studied the reaction produced by various dusts in guinea pigs, and found that there was a distinctly different reaction to coal, flue and transvaal quartz, and flint dust (crystalline silica) in the lungs. The coal dust produced a vigorous reaction and was eliminated much more quickly than the flue or crystalline silica. Unfortunately, he did no work with tuberculosis experimentally, and did not mention whether this difference in reaction had anything to do with the comparatively low incidence of phthisis in coal miners when compared with workers in other dusty trades. In 1919 one of us (4), while studying methods to reduce the resistance of the guinea pig to tuberculosis, used, among other substances, ground glass and lamp black for this purpose. Lamp black, injected subcutaneously and coincident with tubercle bacilli, had a distinct retarding influence, while finely pulverized glass had a markedly accelerating action, though not sufficient to be available for practical use in hastening the guinea pig diagnosis for tubercle bacilli in pathological fluids. At that time it was stated that "it is evident from the experiments reported that regardless of the mechanism, whether it be the reaction produced or the inherent antiseptic properties introduced with the coal or soot, these have a retarding influence upon the local development and spread of tuberculosis in the guinea pig."

In 1922 Willis (5) reported an elaborate study on the influence of the inhalation of coal dust on tuberculous infection in guinea pigs as a continuation of previous studies on pneumonokoniosis. Very finely sifted soft-coal dust was used for inhalation in guinea pigs and the animals were exposed to this for varying periods four and five days a week for three hours a day up to twelve months. Thirty-two of the animals, which had been exposed for from three to twelve months, together with 8 normal guinea pigs, were inoculated subcutaneously in the right groin, each

with 0.1 cc. of an emulsion of virulent human tubercle bacilli, and coal dust was continued for thirteen weeks after inoculation, when all the animals were examined. When thus infected the guinea pig develops relatively scanty pulmonary lesion until late.

There is little that is atypical in the development of tubercle in the lungs of animals exposed to dust. Some lungs in this experiment escaped infection entirely,—in normal animals and in those which had been exposed to dust. Some were also found in both series with a more extensive process than the norm for each. Organ for organ, the lungs which contain dust show on an average a larger number of tuberculous areas (about one-third more in a count of six lungs in each series) than those without dust. . . . . The tuberculous process is practically always extensive in the tracheobronchial lymph nodes in infected guinea pigs and is apparently uninfluenced by previous exposure of the animal to dust. As regards the size of the infected nodes, the extent of the lesion and the amount of tissue destruction, the situation of the lesion in the nodes and the amount of replacement tissue, the process is not greatly different in dusted and nondusted animals. This is not surprising in view of the fact that there is no production of fibrous tissue in these nodes after exposure to dust for as long as a year.

After one year's exposure to coal dust there was no fibrosis in the lungs or tracheobronchial nodes. In guinea pigs living an ordinary cage life of two years or more and not dusted experimentally, there was in comparison some degree of fibrosis in the tracheobronchial nodes. Willis is inclined to view this as a response rather of time than to mere quantity of dust and that soft coal is not as irritating to the tissues as it is thought to be by some observers. Tubercle bacilli and dust particles tend to become located in the same anatomic situation, and the presumption is that the same mechanical and physiological forces, which tend to place the one foreign body, operate in the same manner toward localizing the other. In discussion Willis states:

There is probably some basis for the contention of Beattie, Haythorn and others that the fibrosis which develops in response to the presence of certain dusts would tend to limit the spread of the infectious process and should be regarded as protective in that sense. But the converse is equally true: namely, that the fibrosis would also tend to focalize and to hold bacilli because lymph drainage would be interfered with; so while one would find less extensive spread of infection from a focus in a dusted lung, he might expect to find *a larger number of foci* and *possibly larger foci* scattered through the organ.

Willis finally concluded that after infection tubercle develops somewhat more abundantly in lungs of animals exposed to dust than in those of normal animals: the ratio is about three to two.

It is unfortunate that Cesa-Bianchi (6) could not have detailed his experiments more fully when he reported them in 1913, since he leaves a great deal to be desired in the way of relating the exact technique used for infecting his animals and the detailed findings. He reports on only a few selected animals from his series. However, he draws very definite conclusions, which apparently apply uniformly to all the substances (dusts) used by him. He used talc, gypsum, anthracite coal dust, cement, sand and a number of other substances. Evidently his main conclusions are drawn from guinea pig experiments even though he also used rabbits in his earlier work. The animals were allowed to inhale the dusts two to four hours daily for eight to ten weeks. Two strains of virulent human tubercle bacilli were used for infecting, by first weakening them by drying and heating. The modes of infection were by the respiratory tract, and by subcutaneous, intraperitoneal and intravenous inoculation. Twelve guinea pigs were used for each dust studied, 2 serving as uninfected controls, the remainder receiving an intravenous, intraperitoneal, subcutaneous or intratracheal (?) inoculation of 0.1 to 0.01 loop of the weakened bacilli, an equal number of controls being likewise inoculated. The inhalation method of infection was discontinued because it possessed no apparent advantages and was dangerous. It is concluded that the continued inhalation of dusts, especially those possessing a mechanical action, does not cause severe changes in the air passages and pulmonary parenchyma; but, in spite of this, these inhalations cause a diminished resistance of the lung tissue to infectious agents (he believes that the infectious agent may be of any nature, including tubercle bacilli, the only one he worked with); and that they prepare a favorable medium for their development. In the guinea pigs receiving prolonged dust inhalations the specific tuberculous lesions were found almost entirely in the lungs and their tributary lymph nodes; and this was true regardless of the mode of infection; while in the controls a rapid generalized tuberculosis developed which affected the lymph nodes, and then the liver, spleen and serous surfaces, and only rarely the lungs, without producing, under ordinary circumstances, a diffuse pulmonary tuberculosis, and more rarely cavity formation. The guinea pigs inhaling dust developed a severe and almost always fatal pulmonary tuberculosis. No differences were noted between the action of the coal dust and that of other dusts.

The localization of anthracotic pigment around tubercles in man (Klotz, Haythorn (7)), and of inhaled and injected particulate carbon matter (Haythorn, Foot (8), and Corper and Robin (9)), experimentally, is well established; but it is surprising that a study of the effect of maximum nonlethal amounts of carbon, inhaled and injected, upon experimental pulmonary tuberculosis has not been stressed, in view of the fact that carbon, as lamp black, has a definite local inhibiting effect on tuberculosis. It is admitted that, at the time the earlier experiments, cited above (4), were performed, on guinea pigs, which revealed an inhibiting or retarding influence of soot upon the spread of tuberculosis from the local subcutaneous site of infection, the view was entertained, but not expressed, that the supposed antiseptic properties of the soot played a part in these findings; still this feeling made further study highly desirable and it is for this reason that the following experiments were performed with soot and india ink, the former to be inhaled and the latter to be given by injection for the purpose of analyzing, if possible, the factors concerned in the retarding effect of carbon upon tuberculosis, as was found by one of us previously.

The initial experiment was planned rather elaborately, to gain information as to whether inhaled carbon, as soot (prepared by burning xylene), acted differently on pulmonary miliary tuberculosis in rabbits from carbon in liquid suspension, as india ink, given intravenously, and whether their localization around the tubercles differed and what undesirable and conflicting features might follow their use. If a consistent effect upon the tuberculosis was thus obtained, it was intended to repeat the findings in more accurately planned experiments and to, as far as possible, analyze this effect and thus pave the way for further study of possible therapeutic importance. All the lungs were studied macroscopically and microscopically, in order to check the findings as far as possible. The animal of choice throughout was the rabbit, mainly because this animal could be given repeated intravenous injections of liquid suspensions of carbon and because a nonprogressive and nonfatal pulmonary miliary tuberculosis could be produced by intravenous inoculation of human tubercle bacilli, while bovine bacilli gave rise to a progressive and fatal miliary pulmonary tuberculosis. There was also the added advantage that the tubercles in the lungs were all primary, uncomplicated by much tuberculosis elsewhere in the body (so commonly seen in the guinea pig), and were thus desirably located for both inhalation and intravenous studies.

EXPERIMENT 1

This experiment was planned to include the effect of the inhalation of soot or smoke, prepared by burning pure xylene in the air, as well as the effect of carbon in liquid suspension (as india ink) given intravenously, upon human and bovine pulmonary miliary tuberculosis in rabbits.

In the inhalation experiments the rabbits were placed in a large glass-walled box, into the bottom and at one end of which there entered the narrow end of a large metal funnel. Ample ventilation was supplied through the sides and top of the smoke-chamber, and the smoke or soot from a few cubic centimetres of burning xylene was permitted to enter the chamber through the funnel. The smoke cloud was so dense that a small electric bulb was definitely dimmed. The animals tolerated a daily exposure of about thirty minutes for twenty to thirty days, although at the end of this time they began to loose their appetite, and consequently lost weight. Longer daily periods of inhalation or too prolonged an interval, exceeding thirty days, of exposure resulted in a "snuffles" type of pneumonia or marked congestive pneumonia. At times, an individual rabbit would not do well on daily exposures and these were then placed in the smoke-chamber only every other day. The first part of experiment 1 was planned mainly for orientation, and especially to learn the disposition of carbon inhaled in fine suspension (as soot) in the body, and in particular with relation to the tubercles in the lungs, as compared to the disposition of carbon (in india ink) given by intravenous injection, while the second part of experiment 1 aimed to determine the effect of carbon administered in the two above manners upon the tubercles in the lungs. Although at the termination of the experiment it was realized that, because of the individual variations of the animals and the short period of experimentation, not all the information desired had been obtained, this preliminary study yielded many points of value for the subsequent part of the study. In general the plan of the first part of experiment 1, although the course of the tuberculous infection which proved too rapid for the purpose modified this to a marked degree, was as follows:

1. Rabbits were given a single intravenous inoculation of bovine (0.1 mgm.) tubercle bacilli ten days before the inhalation of xylene soot which was continued for ten and twenty days, respectively, in two separate sets of animals.

2. Rabbits were given a single intravenous inoculation of bovine tubercle bacilli on the day of initiation of exposure to xylene soot for ten, twenty and thirty days, respectively, in three separate sets of animals.

3. Rabbits were given a single intravenous inoculation of bovine tubercle bacilli ten, twenty or thirty days after the initiation of the inhalation of xylene soot, which was continued for ten to twenty days more.

This entire series was exposed daily to xylene soot for 30 minutes. The above plan was then duplicated for the series to be given the intravenous injections of india ink instead of the inhalation of carbon. This series was given daily injections of india ink (*Higgins' Eternal*) in amounts of 2 cc. of a dilution of 1 to 5 in sterile salt solutions. The ink was sterilized each time before injection by boiling for five minutes. (See table 1.)

TABLE 1

The tuberculous involvement and pulmonary distribution of carbon following a single intravenous injection of bovine tubercle bacilli and the inhalation or intravenous injection of carbon over long periods of time in rabbits

PERIOD OF CARBON TREATMENT WITH RELATION TO INFECTION	CARBON GIVEN BY INHALATION (AS XYLENE SOOT)			CARBON GIVEN BY INTRAVENOUS INJECTION (AS INDIA INK)		
	TIME OF EXAMINATION OF ANIMAL AFTER INFECTION	Pulmonary tuberculous involvement†	Pulmonary disposition of carbon, macroscopic**	TIME OF EXAMINATION OF ANIMAL AFTER INFECTION	Tuberculous involvement	Pulmonary disposition of carbon, macroscopic
	days			*days*		
Carbon given 10 days after infection	d 27 (16)*	4^3	0—	d 19 (8)	4^3	xxx
	d 25 (14)	4^3	0—	d 23 (10)	4^3	xxx
	d 23 (12)	4^3	0—	d 23 (12)	4^3	xxx
	d 21 (10)	3^3	0—	d 25 (14)	4^3	xxx
	d 18 (8)	3^2	0—	d 17 (6)	4^3	xxx faint
	d 27 (10)	3^3	0—	d 10 (0)	4^3	0—
	d 20 (9)	4^3	0—			
Carbon begun coincident with infection	k 10 (9)	3^1	0—	d 5 (4)	0	0
	d 22 (20)	3^3	0—	d 20 (10)	4^3	0—
	d 4 (3)	0	0—	k 10 (9)	3^2	xxx faint
	k 19 (18)	3^3	0—	d 22 (21)	3^2	xxx dark
	d 18 (10)	3^2	0—	d 20 (19)	3^1	xxx dark
	d 24 (23)	4^3	xxx slight	d 15 (14)	3^1	xxx moderate
	k 13 (10)	3^1	0—	d 23 (22)	3^3	xxx moderate
	d 27 (20)	4^3	xxx slight	d 8 (7)	1^1	0—
	d 23 (23)	4^3	0—	d 20 (19)	3^2	+x
	d 16 (15)	2^2	0—	d 13 (10)	3^1	+x questionable
	d 16)15)	1^3	0—	d 8 (7)	0	0
				d 20 (19)	3^2	+xx

* "d" indicates the animal died and "k" indicates that the animal was killed on the day specified. The number in parentheses indicates the number of days that the animal was given soot inhalation or intravenous injections of carbon as india ink.

** The macroscopic pulmonary distribution of the carbon in the lungs is graded on the basis of the density of the ring around the tubercles and approximate number of tubercles surrounded by the carbon. Plus signs of the first marking in this column indicating the density of the carbon ring as follows: 0 = no carbon visible macroscopically, + = a moderate carbon ring and ++ = a dense carbon ring; the multiplication signs in the second figure in this column indicating the approximate number of tubercles around which the carbon rings are found as follows: — = carbon rings absent macroscopically, x = carbon rings around about 50 per cent of the tubercles, xx = carbon rings around all the tubercles, and xxx = the carbon diffusely spread throughout the lungs so that ring formation was not discernible.

† The pulmonary tuberculous involvement is graded on the basis of the approximate number and size of the tubercles, the cardinal numbers indicating the number of tubercles as follows: 0 = no visible tubercles, 1 = 1 to 10 in entire lungs, 2 = 10 to 100 in entire lungs, 3 = over 100, and 4 = a diffuse pneumonic tuberculosis. The exponents indicate the approximate size of the tubercles as follows: 1 = up to 0.5 mm. in diameter, 2 = from 0.5 to 1.0 mm. in diameter, 3 = over 1 mm. and up to 2 mm. in diameter, and 4 = over 2 mm. in diameter.

TABLE 1—*Continued*

PERIOD OF CARBON TREATMENT WITH RELATION TO INFECTION	TIME OF EXAMINATION OF ANIMAL AFTER INFECTION	CARBON GIVEN BY INHALATION (AS XYLENE SOOT)		TIME OF EXAMINATION OF ANIMAL AFTER INFECTION	CARBON GIVEN BY INTRAVENOUS INJECTION (AS INDIA INK)	
		Pulmonary tuberculous involvement†	Pulmonary disposition of carbon, macroscopic**		Tuberculous involvement	Pulmonary disposition of carbon, macroscopic
	days			*days*		
Carbon initiated 10 days before infection	k 9 (10)	3[1]	0—	d 18 (20)	3[3]	xxx moderate
	k 13 (10)	3[1]	0—	k 19 (20)	3[3]	xxx moderate
	d 26 (20)	4[3]	0—	k 14 (10)	3[2]	xxx slight
	d 18 (20)	3[3]	0—	d 22 (20)	4[3]	xxx moderate
	k 19 (10)	4[3]	0—	k 19 (10)	3[3]	0—
	d 20 (10)	3[3]	0—	d 29 (20)	4[3]	xxx moderate
	k 19 (20)	3[3]	0—	k 10 (10)	3[1]	0—
	d 7 (16)	1[1]	0—			
Carbon initiated 20 days before infection	d 23 (20)	4[3]	0—	d 19 (20)	3[3]	xxx moderate
	k 10 (10)	3[1]	0—	k 19 (10)	4[3]	0—
	d 8 (20)	1[1]	0—	d 27 (20)	3[3]	xxx moderate
	d 15 (10)	1[1]	0—	k 12 (10)	3[1]	0—
	d 22 (10)	3[3]	xxx very faint	d 20 (10)	3[3]	0—
				d 18 (20)	3[2]	xxx marked
				k 14 (10)	2[3]	0—
Carbon initiated 30 days before infection	k 30 (20)	3[3]	xxx moderate	d 30 (10)	4[3]	xxx moderate
	d 11 (20)	1[1]	0—	k 29 (10)	3[3]	xxx localized especially around little tubercles but not around large tubercles.
				k 30 (20)	3[3]	xxx moderate
				k 30 (20)	3[3]	xxx moderate
				k 30 (10)	4[3]	xxx very faint

A microscopic examination of all the inhalation lungs recorded in table 1 revealed traces of carbon in some of the lungs which were negative microscopically, but it was difficult to determine, when pigment was small in amount, whether this was ordinary anthracotic pigment of spontaneous origin or due to the inhalations. There were, however, sections, especially those taken from some of the animals that had received the carbon inhalations for the longer intervals, that contained more carbon than is normally seen in spontaneous anthracosis in these

animals, and this was definitely due to the inhalations given, yet it was not visible macroscopically. In conformity with previously noted findings, recorded with inhaled carbon as soot (10), there was observed no regularity in the distribution of the carbon pigment within the lungs, many fields being entirely free from it, while in others it was found localized in comparatively large amounts; again, there were many tubercles around which no carbon could be found, while others were surrounded eccentrically or completely. The microscopic findings did not permit deductions as to the possible mechanism of the immediate distribution in the lung tissues, following the inhalation of particulate matter in general, although it is well known that the final lodgment is in the lymphoid tissues. It also seemed that the inhaled carbon reaching the alveoli and finer air divisions, which is the carbon most likely to be carried into the lung parenchyma, was irregularly localized in these terminal respiratory divisions.

Microscopic examination of all the lungs from the rabbits, given the intravenous injections of carbon as india ink, showed the carbon to be usually regularly distributed throughout the lungs, even after short periods of daily intravenous injections. In the uninvolved portions of the lungs the distribution was fairly regular, but in the tuberculous areas the carbon was found mainly at the periphery of the tubercles, while in the acute tuberculous pneumonic areas there was very little. Microscopically, carbon was found even in the lungs which macroscopically had been marked negative. We had hoped, when the first part of experiment 1 was planned, to be able to note certain differences in the distribution of the carbon, especially with relation to the tubercles in the animals in which carbon administrations were initiated before infection, but the acute character and rapidity of development of the pulmonary disease precluded this possibility.

A careful analysis of the findings in table 1, even though controls were omitted, seems to bear out the general idea that the carbon in the lungs has a retarding influence on the tuberculosis developing in them. This idea was, however, put to more severe test in the second part of experiment 1. In brief, this part of the experiment was planned to determine the effect of inhaled and intravenously injected carbon upon the development of human (nonprogressive) and bovine (progressive) pulmonary miliary tuberculosis in the rabbit. A total of 50 rabbits was used, one-half given an intravenous inoculation of 0.5 mgm. of virulent human tubercle bacilli ("Gluckson") in fine suspensions and the other

half an intravenous inoculation of 0.1 mgm. of virulent bovine bacilli ("bovine virulent"). In each set 5 rabbits served as controls; 5 were given xylene soot inhalations for thirty minutes daily, beginning ten days before infection and continued throughout the experiment; 5 were given xylene soot inhalations fifteen minutes daily, begun coincident with infection and continued throughout the experiment; 5 were given intravenous india ink injections (2 cc. of a 1 to 5 dilution) daily, begun ten days before infection and continued throughout the experiment; and 5 were given intravenous india ink injections, begun coincident with infection and continued throughout the experiment. The findings in this experiment are recorded in table 2.

The second part of experiment 1, recorded in table 2, brought out several interesting features. Carbon, inhaled as soot, generally required some time before it was visible macroscopically in the lungs at all, while later it localized in ring form around many, but not all, of the miliary tubercles. If the tuberculosis was of a massive pneumonic type the carbon did not localize to any extent, but merely gave a dark gray tinge to the lungs. Microscopically, it was absent from the pneumonic areas, while it was found around many of the individual tubercles, though irregularly distributed. Carbon, injected intravenously as india ink, could not be seen in the lungs macroscopically shortly after initiation of the injections, but as the injections were continued the lung took on a diffuse dark gray hue. The liver and spleen always retained more carbon than the lungs, while the kidneys had a gray hue only after prolonged administration of the india ink. The bone marrow and lymph nodes also received a goodly proportion of the carbon following intravenous injection. Microscopically, the carbon in the lungs was frequently found uniformly distributed throughout the parenchyma, but the centres of tubercles were strikingly free from it in all sections and there was very little carbon in the pneumonic areas. Many sections also revealed a striking lack of uniformity in pulmonary distribution. The spleen almost always contained far more carbon than the lungs, but the trabeculae and germinal centres were free from it. The liver contained about as much carbon as the spleen, but it was localized mainly at the periphery of the lobules and was scanty around the central vein. In general, the carbon distribution, macroscopically, in these organs, following intravenous injection, followed that noted by Oettinger (11) for bacteria by plating methods. He determined the approximate numbers of several bacteria in the lungs, liver, spleen and blood for short

TABLE 2

The effect of carbon by inhalation and intravenous injection upon pulmonary miliary tuberculosis in the rabbit

METHOD OF ADMINISTRATION OF CARBON	INITIATION OF CARBON ADMINISTRATION WITH RELATION TO INFECTION	TIME IN DAYS OF EXAMINATION OF ANIMAL AFTER INFECTION	PULMONARY FINDINGS AFTER INTRAVENOUS INJECTION OF 0.5 MGM. OF VIRULENT HUMAN TUBERCLE BACILLI "GLUCKSON"		TIME IN DAYS OF EXAMINATION OF ANIMAL AFTER INFECTION	PULMONARY FINDINGS AFTER INTRAVENOUS INJECTION OF 0.1 MGM. OF VIRULENT BOVINE TUBERCLE BACILLI ("BOVINE VIRULENT")	
			Tuberculous involvement	Macroscopic distribution of carbon		Tuberculous involvement	Macroscopic distribution of carbon
		days			*days*		
	Controls not given carbon	k 30	2[2]	—	d 25	4[3]	—
		d 19	1[1]	—	d 23	4[3]	—
		k 30	2[3]	—	d 23	4[3]	—
		k 30	2[1]	—	d 21	4[3]	—
					d 18	4[3]	—
Inhalation as xylene soot, 15 minutes daily	10 days before infection and continued throughout experiment	d 8	1[1]	0—	d 22	4[3]	xxx
		k 30	2[1]	++xx	d 19	4[3]	xxx
		k 30	2[2]	+xx	d 24	4[3]	xxx
		k 30	2[1]	++xx			
		k 30	2[3]	+xx			
	Coincident with infection and continued throughout experiment	k 30	2[1]	++xx	d 23	4[3]	xxx pale
		k 30	2[2]	++xx	d 21	4[3]	xxx
		k 30	2[1]	++xx	d 20	4[3]	xxx
		k 30	3[1]	++xx	d 20	4[3]	xxx
		d 7	1[1]	0—	d 19	4[3]	xxx
Intravenous injection daily of 2 cc. of india ink (diluted 1 to 5)	10 days before infection and continued throughout experiment	d 17	3[1]	xxx	d 25	4[3]	xxx
		k 30	2[1]	x	d 25	4[3]	xxx
		d 17	3[1]	xxx	d 21	4[3]	xxx
					d 23	4[3]	xxx
					d 24	4[3]	xxx
	Coincident with infection and continued throughout experiment	k 30	2[1]	+xx	d 23	4[3]	xxx
		k 30	2[2]	xxx	d 21	4[3]	xxx
		k 30	2[3]	++xx	k 25	4[3]	xxx
		k 30	2[2]	+xx	d 23	4[3]	xxx
		k 30	2[1]	+xx	k 25	4[3]	xxx

intervals after intravenous injection, and found a great preponderance of bacteria in the spleen and liver as compared with the lungs, although the detailed figures varied considerably in the different rabbits and at different times.

Lund, Shaw and Drinker (12) have given us some conception of the quantitative distribution of particulate matter (manganese dioxide) following intravenous injection in different species of animals and have excellently reviewed the literature on the subject. On the basis of 100 gm. of wet tissue, they found the liver in rabbits to contain 0.178 mgm., the spleen 0.054 mgm. and the lungs 0.036 mgm., while on the basis of the total manganese dioxide injected the liver contained over 80 per cent and the lung and spleen less than 5 per cent. They point out that most observations agree with their manganese dioxide findings and cite Hopkins and Park (1918) as obtaining the same relative proportions when using streptococci in rabbits. There is also a difference between the animals tested, especially most striking as between the cat and rabbit during the early intervals after intravenous injections.

Drinker, Shaw and Drinker (13) also studied the rate of disappearance of manganese dioxide and manganese metasilicate from the organs of cats and rabbits after intravenous injection. The former was eliminated from the body in one week. As the process of removal goes on there is a transfer of manganese from the lungs to the liver. In rabbits the removal was more rapid, owing to the fact that in these animals the lungs are not involved and the whole process of removal from the blood is carried on by the liver. The disappearance of manganese metasilicate is slower and is complete in about fifty days. If, however, the proportionate rate of disappearance from the lungs and liver of rabbits is considered, it was noted that the lungs lose the manganese dioxide only about as rapidly as the liver. The same holds true for manganese metasilicate. It is interesting that, in the cat, with the more insoluble manganese metasilicate there is no shift from the lungs to the liver as occurs with manganese dioxide. The elimination of these substances from the lungs is not explained.

As seen from microscopic examination, which cannot be as accurate as chemical analysis but, under certain circumstances, may be of definite, though only relative, value, table 3 reveals the relative average distribution of carbon microscopically in the lungs, liver, spleen and kidneys of some of the rabbits used in the first and second part of experiment 1 (table 2), chosen at random, the relation being based primarily on the amount found in the lungs. The lungs proved to be more variable in carbon content after intravenous injection than any of the other organs examined.

Regarding the findings pertaining to the effect of the carbon in the lungs upon the tubercles of the rabbits recorded in table 2, it may be noted that when the infection was rapidly progressive, as in the animals given bovine bacilli, there was no perceptible difference between the controls and the animals receiving the carbon either by inhalation or injection; but the series that were infected with the human bacilli revealed what appeared to be a slight, though definite, retardation of development of the tubercles in the carbon lungs as compared to the lungs of the controls, the intravenous series proving, in this respect,

TABLE 3

The relative average microscopic distribution of carbon in the liver, spleen and kidneys, compared with the lungs of rabbits following repeated intravenous injections of india ink

AVERAGE DAYS INJECTED	APPROXIMATE COMPARATIVE AMOUNT OF CARBON SEEN IN MICROSCOPIC FIELDS				
	Number of specimens examined.	Lung	Liver	Spleen	Kidney
10	6	Slight*	2.3†	2.3	Slight trace
17.6	23	+	3.1	3.1	Trace
17.7	20	++	3.2	3.3	Trace
19.0	3	+++	3.6	3.3	+

* All the gradings of the amount of carbon present in a section of tissue can only be relative and are graded from 0, indicating a complete absence of carbon, to ++++, a large amount and the maximum seen in any field of the sections studied.

† The numerals and fractions indicate the average of all the gradings of the carbon in the sections, according to the above markings, 0 to ++++, in the tissue under consideration.

more striking than the inhalation series. The effect was mainly upon the size, rather than the number of the tubercles, which is what might be expected when it is considered that the initial seeding determines the number of tubercles primarily.

EXPERIMENT 2

This experiment was planned to more accurately determine the effect of the inhalation or intravenous injection of carbon upon pulmonary miliary tuberculosis in the rabbit in view of the experiences obtained from experiment 1 and upon a larger series of animals. It was further considered desirable since the bovine infection in the second part of experiment 1 proved too severe, and thus led to findings of no definite value, except possibly to indicate that a severe progressive infection is not influenced in its course by the presence of carbon in the lungs. There also seemed to be need for a more prolonged study than in experiment 1.

The experiment included 60 rabbits, half of which were given an intravenous injection of 0.001 mgm. of tubercle bacilli "Bovine virulent" and the other half an intravenous injection of 1 mgm. of human tubercle bacilli "Gluckson." Ten of each set were infected only as controls; 10 were given inhalations of xylene soot for 15 minutes daily (about 1 to 2 cc. of xylene being burned to fill the exposure chamber) initiated about 10 days before infection and continued throughout the experiment; and 10 were given daily intravenous injections of india ink (1 cc. of 30 per cent in physiological salt solution, boiled prior to each injection). The pulmonary findings at the end of about 37 days were then recorded in the same manner as in experiment 1 and are given in table 4.

The approximate macroscopic gradings of the organs of the rabbits receiving the india ink intravenously are given in table 5. These gradings are on the basis of the depth of color, which compares fairly well with the grading based on the examination of equal microscopic fields, although it must be remembered that, even though this method of grading might give the impression that the distribution of the carbon in the tissues is uniform, this is not the case, as was pointed out previously for the liver, spleen and lung. It must also be remembered that these approximations give no idea of the total organ content in carbon, which can only be ascertained by chemical methods.

Tables 4 and 5 reveal that carbon by inhalation has a slight retarding effect upon the development of tubercles of human or bovine origin in the lungs of rabbits, while carbon given intravenously as india ink has a distinct retarding effect. The latter results in a heavy deposition of the carbon in the liver, spleen and bone marrow, with distinctly less in the lungs and lymph nodes, traces in the heart auricles and kidney (cortex), and no appreciable deposits in the brain, gastrointestinal tract, thyroid and adrenals. The pulmonary deposition of carbon following prolonged intravenous injection is not altered appreciably by the presence of a miliary human or bovine infection.

EXPERIMENT 3

The effect of carbon in culture media upon the growth of tubercle bacilli

In view of the facts that carbon in the lungs retards the development of pulmonary miliary tubercles in rabbits and that carbon in the subcutaneous tissues of guinea pigs retards the systemic spread of tuberculosis in these animals, it was deemed advisable to analyze further the mechan-

TABLE 4

The effect of carbon by inhalation and intravenous injection upon pulmonary tuberculosis in the rabbit

METHOD OF ADMINISTRATION OF CARBON	SET OF ANIMALS	PULMONARY FINDINGS AFTER INTRAVENOUS INJECTION OF			
		1 milligram virulent human tubercle bacilli		0.001 milligram of virulent bovine tubercle bacilli	
		Tuberculous involvement	Macroscopic distribution of carbon	Tuberculous involvement	Macroscopic distribution of carbon
	Controls not given carbon	1^1		2^4	
		1^2		2^4	
		2^1 (30 days)		2^4	
		2^1		2^4	
		1^2		2^4	
		2^1		3^4	
		1^1 (29 days)		1^1 (14 days)	
		1^1 (27 days)		2^1 (24 days)	
		0 (16 days)		1^1 (15 days)	
				1^1 (17 days)	
Inhalation of xylene soot 15 minutes daily	Initiated 10 days before infection and continued until last week of experiment	1^1	++xx	2^3	++x
		2^1	++xx	2^3	+xx
		3^2	+xx	2^3	++xx
		1^1	++xx	2^4	+x
		2^2	++xx	2^4	+x
		Diffuse tuberculosis	xxx	2^4	++xx
		0 (11 days)	xxx	2^4	+x
		0 (10 days)	−	2^4	++xx
		snuffles (18 days)	−	1^1 (14 days)	0
		1^1 snuffles (19 days)	+	0 (18 days)	0

Intravenous injection daily of 2 cc. of india ink (30 per cent)	Initiated 10 days before and continued until last week of experiment	0	xxx along septa	1[4]	+xxx
		2[1]	+x	2[2]	+xxx
		2[1]	+xxx	2[2]	+xxx
		0	xxx	1[2]	+xxx
		0	xxx	1[3]	+xxx
		1[1]	++xx	2[4]	+xxx
		1[2]	xxx	1[3]	+xxx
		0	xxx	1[2]	+xxx
		0 (19 days)	xxx	2[3]	+xx
		1[1]	xxx	0 (12 days)	xxx faint.

Note: All animals were examined on the thirty-seventh day after infection except when otherwise designated by the days in parentheses.

ism concerned, at least in so far as this was possible experimentally *in vitro*. If this action is due to any inherent properties of the carbon this should easily be determined by suitable experiments in which carbon is added to the ordinary culture media, and also by utilizing tissues, containing carbon introduced *in vivo*, as culture media for *in vitro* tests. The general plan of this experiment was as follows:

TABLE 5

Approximate macroscopic distribution of carbon in rabbits given india ink intravenously over long periods of time

INJECTION	LUNG	LIVER	SPLEEN	HEART		KIDNEY	BONE MARROW	BRAIN	GASTROINTESTINAL TRACT	THYROID	ADRENALS	LYMPH NODES
				Auricle	Ventricle							
Human	1*	3	3	1	0	1	3	0	0	0	0	—
	1	3	3	1	0	1	3	0	0	0	0	1
	1	3	3	1	0	1	3	0	0	0	0	2
	1	3	3	1	0	1	3	0	0	0	0	2
	±	3	3	1	0	1	3	0	0	0	0	3
	1	3	3	1	0	1	3	0	0	0	0	1
	1	3	3	1	0	1	3	0	0	0	0	1
	±	3	3	1	0	1	3	0	0	0	0	1
	1	3	3	1	0	1	3	0	0	0	0	±
	1	3	2	1	0	1	3	0	0	0	0	1
Bovine	1	3	3	1	0	1	3	0	0	0	0	—
	±	3	3	1	0	1	3	0	0	0	0	1
	1	3	3	1	0	1	2	0	0	0	0	1
	2	3	3	1	0	1	3	0	0	0	0	2
	1	3	3	1	0	1	3	0	0	0	0	—
	1	3	3	1	0	1	3	0	0	0	0	2
	1	3	3	1	0	1	3	0	0	0	0	±
	1	3	3	1	0	1	3	0	0	0	0	1

* The amount of carbon is graded more on the appearance of the organ in question and is, therefore, only an approximation, but agrees fairly well with that found microscopically in quantity but not in distribution. 0 = no carbon visible, ± = an uncertain amount, 1 = a faint gray tint, 2 = a moderate graying, 3 = a dark gray, and 4 = a distinct blackening of the organ.

Standard suspensions of carbon were prepared: suspension A, containing 0.1 gm. of commercial lamp black in 1 cc. of 7 per cent acacia in 0.9 per cent sodium chloride solution; suspension B, containing 0.1 gm. of coal soot in 1 cc. of 7 per cent acacia saline; and suspension C, containing Higgins' "eternal" black ink, full strength, 1 cc. containing 0.2 cc. of centrifugated (3000 r. p. m.) carbon sediment after adding 9 volumes of acetone to aid sedimentation.

TABLE 6

The effect of lamp black, coal soot and india ink upon the growth of tubercle bacilli on glycerol agar and Dorset's egg medium

FORM OF CARBON ADDED TO MEDIUM	TYPE OF MEDIUM USED	DILUTION OF CARBON TESTED	STRAIN OF TUBERCLE BACILLI TESTED								
			"Human"			"Gluckson"			"Bovine virulent"		
			Amount in cubic centimetres of carbon suspension added to 10 cc. of medium								
			1.0	0.5	0.2	1.0	0.5	0.2	1.0	0.5	0.2
Lamp black (full strength contains 0.1 gm. to 1 cc.)	5 per cent glycerol-agar	Full strength	3, 3*	3, 1	3, 1	3, 2	2, 2	3, 1	3, 3	3, 3	3, 3
		1:10	2, 2	2, 2	2, 2	3, 1	2, 3	2, 3	3, 3	3, 3	3, 2
		1:100	3, 1	2, 2	2, 2	1, 1	2, 1	2, 2	3, 3	3, 2	3, 3
		1:1000	3, 3	3, 2	3, 2	2, 2	2, 2	±, 2	3, 3	3, 3	3, 2
		1:10,000	3, 3	2, 3	3, 2	2, 2	2, 3	2, 3	3, 3	3, 3	3, 3
		Controls without carbon	2, 1	3, 2		2, 2	2, 1		3, 3	3, 3	2, 3
	Dorset's 5 per cent glycerol-egg	Full strength	3, c	3, 4	3, c	3, 3	3, 3	3, 3	3, 3	3, 4	3, 4
		1:10	3, c	4, 3	3, 2	3, 3	3, 3	3, 3	3, c	3, 3	4, 4
		1:100	3, 3	3, 4	3, 4	3, 3	3, 3	3, 3	4, 3	3, 4	3, 3
		1:1000	4, 4	3, 3	3, 3	3, 2	4, 3	3, 3	3, —	3, 3	3, 3
		1:10,000	3, 3	3, 3	3, 3	3, 3	3, 4	3, 3	3, 3	3, 3	3, 4
		Controls	3, 3	3, 2	2, 2	3, 3	3, 2	2, 3	3, 3	4, 2	3, 3
Coal soot (full strength contains 0.1 gm. to 1 cc.)	5 per cent glycerol-agar	Full strength	±, ±	3, 1	2, 1	1, 2	1, 1	±, ±	2, 2	3, 2	3, 2
		1:10	2, 2	2, 1	2, 2	2, 2	±, 0	3, 1	2, 1	2, 3	2, 3
		1:100	1, 2	3, 2	1, 1	2, 2	2, 2	2, 2	3, 3	3, 3	3, 2
		1:1000	±, 1	2, 1	1, 1	1, ±	1, 1	1, 2	3, 2	4, 3	3, 2
		1:10,000	2, 2	2, 1	2, 1	1, 1	1, 0	1, 2	3, 0	3, 3	3, 1
		Controls	2, 1	2, 2		2, 1	2, 1		3, 3	3, 3	2, 3
	Dorset's 5 per cent glycerol-egg	Full strength	0, 0	0, 0	2, 0	0, 0	0, 0	0, 0	1, c	3, 0	3, 1
		1:10	3, 2	3, 3	3, 3	0, 0	3, 3	3, 2	3, 0	3, 3	c, c
		1:100	3, 3	3, 0	3, 2	3, 2	3, 2	3, 3	3, 3	3, 3	3, 3
		1:1000	3, 3	3, 2	3, c	3, 0	3, 3	3, 3	3, 3	3, 2	3, 3
		1:10,000	3, 3	3, 3	3, 3	2, 1	3, 0	3, c	3, 1	0, 0	2, 0
		Controls	3, 3	3, 2	2, 2	3, 3	2, 1	3, 2	3, 3	3, 3	2, 2
India ink (Higgins' full strength, 1 cc. contains 0.2 cc. sediment)	5 per cent glycerol-agar	Full strength	3, 3	3, 3	3, 3	3, 2	2, 2	2, 1	2, 2	3, 3	3, 3
		1:10	3, 3	3, 0	3, 3	2, 2	2, 1	1, 0	3, 3	3, 3	3, 3
		1:100	3, 3	3, 4	3, 3	2, 2	2, 2	2, 1	3, 3	3, 3	3, 3
		1:1000	3, 3	3, 3	3, 3	3, 1	2, 2	1, 3	3, 3	3, 3	3, 3
		1:10,000	3, 2	3, 2	3, 3	2, 2	2, 2	2, 0	3, 3	3, 3	3, 3
		Controls	3, 2	3, 3	3, 3	2, 1	2, 2	3, 1	3, 3	2, 2	3, 3
	Dorset's 5 per cent glycerol-egg	Full strength	3, 3	3, 3	3, c	2, 2	3, c	2, 1	3, 3	3, 3	3, 3
		1:10	3, c	3, 3	3, 3	2, 0	2, 3	2, 1	3, 3	3, 3	3, 2
		1:100	3, 0	3, c	3, 3	2, 2	3, 2	2, 1	3, 0	3, 3	3, ±
		1:1000	3, 3	3, 3	3, 3	2, 1	2, 2	2, c	3, 3	3, 3	3, 3
		1:10,000	3, 0	3, 3	3, 0	2, 2	2, 2	2, 2	3, 0	3, 3	3, 3
		Controls	3, 2	2, 2		2, 3	2, 1		3, 3	4, 2	3, 3

* Two culture tubes were seeded with tubercle bacilli for each dilution of carbon suspension and the readings are given as follows: 0 = no growth after 2 months' incubation, ± = a questionable growth, 1 = a beginning definite growth, 2 = a moderate growth, 3 = a good heavy growth, 4 = an exceptionally good growth, and C indicates that the medium was so contaminated that readings could not be made. Thus 3, 2 indicates that one tube had a good heavy growth, and the other a moderate growth.

Suspensions A, B and C were all sterilized by boiling for thirty minutes to one hour. In the *in vitro* culture tests two types of media were used, namely, 5 per cent glycerol-agar and Dorset's 5 per cent glycerol-egg. A standard amount of 10 cc. of media was used for each culture tube and the following dilutions of suspensions A, B and C added: 1.0, 0.5 and 0.2 cc. of full strength, 1 to 10, 1 to 100, 1 to 1,000, 1 to 10,000 and 1 to 100,000 dilutions in saline acacia. In the case of the agar the requisite amount of suspension was added while the agar was melted, and it was well shaken to ensure complete mixing, and was then slanted and allowed to cool and set. With the egg media the requisite amounts of suspensions were well mixed before inspissating the media for one hour on three successive days at about 90°C. The above culture tubes, including control tubes without carbon in any form, were then seeded with tubercle bacilli, using three separate cultures for this purpose, namely, *Human*, an avirulent laboratory strain of human bacilli, *Gluckson*, a virulent bacillus, and *Bov. Vir.*, a virulent bovine strain, and were incubated at 37°C. for two months, after which they were read and recorded. The results are given in table 6.

Thus, carbon in the form of lamp black, coal soot or india ink added to glycerol-agar or egg media even in fairly large amounts (0.1 gm. in 10 cc. of medium) was found to have no appreciable influence on the growth of human and bovine tubercle bacilli. Coal soot seemed to have a slight effect in the highest concentration, which, however, was not consistent for the three cultures tested and may have been only an accidental effect. Since these findings still lacked correlation with conditions as they exist in the tissues, especially concerning the quantity of carbon present and its intimate distribution, it was considered desirable to grow bacilli upon the various tissues containing carbon after intravenous injection.

In vivo-vitro culture experiment

Tubercle bacilli can be grown only upon inspissated tissues, because fresh tissues usually suffer changes which are destructive to the bacilli. It is usually advisable to add glycerol to the tissue and this was added before inspissation, alone to 5 per cent content, and as glycerol-broth of ordinary glycerol-broth content.

The tissues were obtained from rabbits receiving daily intravenous injections of 5 cc. of 1 to 1 sterile india ink diluted with 0.9 per cent sodium chloride solution (each cubic centimetre containing 0.1 cc. by volume of carbon sediment) for one week. The amount of ink was about the maximum

tolerated dose. The organs containing the larger amounts of carbon (lungs, liver, kidney and spleen) were removed, ground up, mixed with glycerol or glycerol-broth, inspissated for one hour on three consecutive days, and were then seeded with tubercle bacilli and incubated at 37°C. for one month and read. Organs from normal rabbits that had not received carbon injec-

TABLE 7

The effect of carbon contained in inspissated tissues, after the intravenous injection of india ink for one week in rabbits, upon the growth of tubercle bacilli in vitro at 37°C.

STRAIN OF TUBERCLE BACILLI	ADDITION TO TISSUE BEFORE INSPISSATION	CARBON PRESENT OR NOT IN ORGAN USE FOR MEDIUM	ORGAN USED FOR PREPARING INSPISSATED MEDIUM			
			Liver	Spleen	Lungs	Kidneys
"Human"	1 volume 20 per cent glycerol 4x broth to 3 of tissue	+	0, 3, 4, 3*	1, 2	2, c	2, 1, c
		0	1, c, 1, 0	1, 1	3, 1	1, c
	5 per cent glycerol	+	2, 3, 3, 3, 3	3, 2	3, 2, 1	2, 1
		0	3, 0, 2, 3	1, 2, 1	2, 2	1, 2
"Gluckson"	1 volume 20 per cent glycerol 4x broth to 3 of tissue	+	1, c, 3	1, 2	1, 2	1, 0
		−	3, 3, 1, 2	1, 1	2, c	1, 1
	5 per cent glycerol	+	3, 0, 1, 3	1, 2	3, 1	3, c
		−	3, 1, c	1, 1	c, 2	0, 1
"Bov. Vir"	1 volume 20 per cent glycerol 4x broth to 3 of tissue	+	3, 2, c	3, 2	1, 2	2, c
		−	4, 1, c	0, 2	2, 1	3, 2
	5 per cent glycerol	+	2, 1, 2, 1	2, 2	2, 2, 2, 2	1, 2
		−	2, 1, 1	2, ±	1, 0, 1, 2	2, 1, c

* Each number indicates the findings in a single culture tube. The growth of tubercle bacilli upon the medium is graded as previously from 0 = no visible macroscopic growth, ± = a questionable growth, to 4 = an excellent profuse growth; c = the medium was contaminated in this tube and the growth could not be determined.

tions, but which were otherwise treated in a similar manner to the above, were used as controls. The findings given in amount of growth obtained on the inspissated tissues are recorded in table 7.

The findings recorded in table 7 indicate that the carbon in the various tissues (lung, liver, spleen and kidneys) of the rabbit examined had no

inhibitory influence on the growth of human or bovine tubercle bacilli when the tissues inspissated after the addition of glycerol or glycerol-broth were used as media. Inspissated lung, liver, spleen and kidneys, from rabbits which had been injected with india ink also had no appreciable effect upon the growth of the bacilli. The findings were identical to those recorded in table 7 and are, therefore, not recorded.

DISCUSSION

It seems fairly well proved by the above experiments that the retarding influence of the carbon, both in the previously performed experiments on guinea pigs, in which the systemic spread of the disease from the subcutaneous site of injection was retarded as well as the development of pulmonary miliary tubercles in rabbits after the intravenous injection of tubercle bacilli, cannot be due to any inherent antiseptic properties of the carbon in the forms used. It must also be remembered that Willis found that tubercles in guinea pigs' lungs were larger in those having received inhalations of coal dust, entirely opposite findings to those recorded by us for the rabbits' lungs that contain carbon. In just how far the different modes of infection may have played a part it is difficult to determine. It is true that Willis used coal dust, a mixture of complex nature, while we used purer forms of carbon, which may act slightly differently, although it is not believed that this accounts for the diverse findings.

The tubercles produced in the above experiments in the rabbits' lungs were primary, following intravenous injection, while in Willis's experiments they were secondary to subcutaneous infection. It should be interesting to find out whether primary tubercles of the lungs in guinea pigs would act similarly. The fact, however, stands out preëminently that there is an inconsistency between the findings in the guinea pig and rabbit at present. It may be possible that the explanation for this diversity lies in the fact, well established by Krause and his colleagues, of difference in anatomic distribution of the lymphoid tissue in the lungs of the two species of animals. The guinea pig's lung is of the "open type," with ready access to the tributary peribronchial and peritracheal lymph nodes, while the rabbit's lung is "closed" and lymphatic drainage to the tributary lymph nodes is slow and difficult. However this may be, it remains for future experimental studies to determine, if possible, the reason for the retardation of primary pulmonary miliary tuberculosis

in the rabbit and the greater development of the primary pulmonary tubercles in the carbon-containing lungs of the guinea pig, if the latter bears out Willis's findings with secondary or metastatic tubercles. The findings in the rabbit's lungs bear out clinical and pathological findings in man, but this may merely mean that in this respect the anatomy of the rabbit's lungs, in its lymphoid tissue and lymphatic distribution, resembles that in human lungs more closely than that found in the guinea pig. The facts at hand seem to agree with Krause's conception which might easily explain the differences noted, but it remains for further study to disclose the exact detail of this mechanism.

SUMMARY

Carbon inhaled as soot, prepared by burning xylene, is deposited mainly in the lungs of rabbits after prolonged inhalation. The deposition in tuberculous lungs is, however, irregular, not conforming to any definite pattern or rule. There are many areas in the lungs comparatively free, microscopically, from carbon and, likewise, many tubercles only partially surrounded with carbon or free from it. Even though inhalation was initiated twenty days before infection by intravenous injection, the centres of the tubercles were free from carbon.

Carbon, administered in liquid suspension (india ink) daily and intravenously to rabbits for long periods (about forty-seven days), is found deposited mainly in the liver, spleen, bone marrow, lungs, lymph nodes, and, to a slight extent, in the kidneys and heart; the brain, thyroid, adrenals and gastrointestinal tract are relatively free from it. The liver and spleen retain far more carbon than the lungs. The approximate relative distribution, although varying slightly for the individual rabbits used, agrees well with the distribution noted by Oettinger (1908) and Hopkins and Parker (1918), following a single intravenous injection of bacteria, and Drinker and his colleagues (1921), following a single intravenous injection of suspensions of manganese dioxide and manganese metasilicate. The intravenously injected carbon was more diffusely and uniformly deposited in the lungs than the inhaled carbon, although the centres of tubercles were likewise free from carbon, even though carbon injections were initiated ten days before infection.

The development of miliary pulmonary tubercles in rabbits resulting from the intravenous injection of suitable doses of virulent human or bovine tubercle bacilli was definitely retarded by the presence of carbon

in the lungs, resulting from the daily inhalation of soot, prepared by burning xylene, or from the daily intravenous injection of carbon in liquid suspension (india ink). If the intravenous dose of tubercle bacilli was too large, and resulted in a rapid acute pulmonary disease, no visible effect of the carbon was noted. Carbon, as coal soot (0.01 gm. per 1 cc. of medium), lamp black (0.01 gm. per 1 cc.) or india ink (0.02 cc. by volume carbon to 1 cc.), added to 5 per cent glycerol-agar or Dorset's glycerol-egg, has no appreciable effect upon the growth of human or bovine tubercle bacilli, making it seem unlikely that the retarding effect upon the pulmonary tubercles in the rabbit is due to any inherent chemical property of the carbon. Likewise, carbon contained in inspissated tissues obtained from rabbits (liver, spleen, lung and kidneys), having received intravenous injections of india ink for one week (or one month) in maximum tolerated daily doses, had no influence upon the growth of tubercle bacilli. In view of these results and those obtained by Willis, which require repetition in slightly modified form, it seems that the action of the carbon upon tuberculosis is rather to be sought in some action upon the tissues or their lymphatic circulation, as suggested by Krause.

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THE EFFECT OF ARTIFICIAL CIRCULATORY CONSTRICTION ON LOCAL TUBERCULOSIS IN THE RABBIT[1]

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In a previous communication from this laboratory (1) it was shown that 3 per cent carbon dioxide causes some inhibition of growth of the tubercle bacillus in the test tube and that 15 per cent is tuberculocidal. Tubercle bacilli also failed to grow in a carbon dioxide-free atmosphere. Cultures, buried in the tissues of animals and thus subjected to the carbon dioxide concentration of the body, are definitely inhibited, while other cultures similarly buried, except that ingress of atmosphere air is permitted, show no inhibition. At the time of publication of this work (1921) it was pointed out that the significant feature was that the concentration sufficient to definitely inhibit bacillary growth, namely 5.5 per cent, occurs normally in the human body.

Thus far, however, our evidence might be considered more as circumstantial and, even though encouraging, as requiring more accurate analysis and, if possible, a detailed study of the bacilli in the tissues themselves. At first glance this might appear rather simple, especially now that a tissue-culture technique is available, but anyone who has tried to manipulate carbon dioxide in accurate amounts and under stable conditions will soon realize the magnitude of the task. An attempt to reproduce artificially the chemical gaseous and liquid relationships of carbon dioxide, sodium bicarbonate and buffer salts to one another, as they occur in the body, over the long periods of time necessary for experimentation, proved too complicated with present facilities and had to be abandoned after numerous failures. To grow tubercle bacilli on media of different concentrations of sodium bicarbonate also proved discouraging because these media, tending to become alkaline by losing carbon dioxide, introduced marked inaccuracy and left us in doubt as to whether the alkalinity itself or the sodium bicarbonate inhibited growth. Finally, by using the basic phosphate of sodium in media, and neutralizing this by

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passing carbonic acid gas through the media until they were neutral (about pH 7 to 7.5 to phenolsulphonphthalein), fairly stable media were obtained which showed that in the higher concentrations carbon dioxide in combined salt form, even in the presence of atmospheric air, slightly inhibited the growth of tubercle bacilli, as compared with media without the combined carbon dioxide.

That the carbon dioxide concentration in the various parts of the body and under different conditions varies at different times cannot be doubted, but an accurate standardization of these conditions applicable to experimental studies is still lacking. It was for this reason that a rather drastic artificial precedure, directly applied to the animal, was resorted to. In order to get an increased carbon dioxide content of a part of the body suitable for inoculation and repeated observation, and still available for suitable controls, the frequently used and well known method of inoculation of the auricle of the rabbit's ear was chosen. It is known that the reaction to local tubercle may markedly vary in different animals, but different inoculations of the same nature in the same animal are usually fairly uniform and serve far better for comparative studies. Rabbits' ears were found especially advantageous, since one ear could readily be constricted by means of a rubber band to produce a stasis hyperemia with distinct cyanosis and, as analyses revealed, an increased carbon dioxide content of the plasma. Unfortunately, it was not possible to obtain arterial and venous blood separately, but the blood from the constricted and nonconstricted auricles could easily be compared.

An examination of the blood from the constricted and nonconstricted auricles, and, coincidently, venous and arterial blood gave the figures in 12 rabbits recorded in table 1.

As shown in table 1, the plasma from the constricted auricle may contain from 10 to 50 per cent more bicarbonate (the latter amount only in exceptional cases) than that from the normal ear. The usual average above normal is about 10 to 20 per cent. The blood from the normal auricle contains about the same amount of plasma bicarbonate as venous blood, although frequently the value lies between the venous and arterial plasma figures. This is rather to be expected when it is realized that the blood obtained from the ear was really a mixture of arterial and venous bloods.

Since it was possible that the plasma-corpuscle relation of the blood may have suffered changes in the congested ears, the corpuscle volume of the blood taken from the auricles of 7 rabbits, in which one was con-

TABLE 1

The effect of constriction cyanosis of the auricles of the rabbits' ears on the carbon dioxide content of the plasma

Cubic centimetres of CO_2 at 0° and 760 mm. bound as bicarbonate by 100 cc. of plasma

RABBIT	VENOUS BLOOD FROM EXTERNAL JUGULAR VEIN	ARTERIAL BLOOD FROM THE CAROTID ARTERY	BLOOD FROM THE CONGESTED AURICLE	BLOOD FROM THE NORMAL AURICLE
1			43.9 edema	39.3
2	24.9	16.2	32.8 edema	26.5
3	30.5	23.3	47.2 edema	30.5
4		30.5	46.4	42.3
5	27.3	12.2	25.7	19.4
6	33.7	24.9	39.2 edema	28.1
7	36.0	27.3	40.8 edema	32.8
8	28.1	15.4	24.9	21.7
9	30.5	17.8	34.4 edema	27.3
10	24.9	20.2	30.5 edema	23.3
11	27.3	18.6	36.0 edema	29.7
12	27.3	17.0	34.4 edema	28.1

TABLE 2

The corpuscle volume of blood obtained from normal and constricted (nonedematous and edematous) auricles of rabbits

RABBIT	CONDITION OF AURICLE	CORPUSCLE VOLUME* (TOTAL BLOOD CONSIDERED AS 1)	CUBIC CENTIMETRES OF CO_2 AT 0° AND 760 MM. BOUND AS BICARBONATE BY 100 CC. PLASMA
1	Normal	0.23	40.0
2	Normal	0.31	35.3
3	Normal	0.26	32.3
4	Normal	0.31	36.9
5	Congested	0.31	28.0
	Congested and edematous	0.28	32.8
6	Congested	0.31	26.5
	Congested and edematous	0.33	28.4
	Congested	0.30	24.9
	Congested and edematous	0.27	32.8
8	Congested	0.40	18.6
	Congested and edematous	0.32	28.0
9	Congested	0.20	26.5
	Congested and edematous	0.16	34.5

* The corpuscle volume was determined by taking a measured amount of oxalated blood, centrifugating at about 3000 r.p.m. and measuring the height of the total blood and corpuscle columns. The figures were then reduced to comparative values by arbitrarily considering the total blood column height as 1 and finding the corpuscle-column height corresponding to this.

gested to the point of marked edema and the other only slightly congested, was examined, and for comparison the blood from the nonconstricted auricles of 4 normal rabbits was also examined. The plasma bicarbonate was determined for all at the same time. The findings are recorded in table 2.

It is to be noted in table 2 that the corpuscle-plasma relation is usually decreased slightly and the plasma bicarbonate increased in the blood taken from the congested and edematous as compared to that taken from the nonedematous congested auricles.

Since the above procedure is a modification of Bier's stasis hyperemia, a glance at the literature on this subject might elucidate the by-effects of the procedure alone, and throw some light on its purely physiological accompaniments.

Donati and Delfino (2) found that after constriction of the auricles of rabbits incisions of the cartilages almost invariably healed in much less time than did similar incisions of nonconstricted auricles. The constricted auricles seemed better nourished; the processes of repair were exactly the same in both auricles. The effect of stasis hyperemia has been studied experimentally by Carl (3) in streptococcus infections of rabbits' auricles. The stasis auricle showed much edema and thickening histologically; rupture of the epidermis, however, never occurred. The veins were especially dilated and the arteries partially though not constantly filled; however, rupture of a vein with small accumulations of blood was never seen. Venous thrombosis occurred when the stasis was long-continued. Capillary rupture was seen at times. The epidermis suffered practically no changes; but the subcutaneous tissues were edematous, and, in some cases, the infection was slightly influenced, although not when it was severe. Frankenheim (4), (5), with stasis hyperemia of the hind legs of rabbits, found the lesions produced by staphylococci and streptococci to be larger than in the nonconstricted leg, while bone lesions were also aggravated rather than benefited by the treatment. Aronade and Falk (6) found that stasis hyperemia enhanced local tuberculin reactions in children and frequently caused an entirely faded reaction to flare up again. It also induced capillary hemorrhages at the site of the tuberculin reaction. Although in the early days of Bier's hyperemia treatment the method was used in tuberculosis clinically, it was, however, discontinued. In 1906 Baumgarten (7) reported studies from his laboratory on the effect of stasis hyperemia upon experimental tubercle bacillus, staphylococcus and anthrax infections, that were intraärticular and subcutaneous. The stasis in tuberculosis was of 1 to 2 hours' duration daily for weeks, in staphylococcus infections of 12 to 24 hours' duration with pauses of 24 hours, and with anthrax a single continuous

application of 24 to 48 hours. In anthrax the stasis completely inhibited infection if the dose was not excessive. With staphylococcus infections results were less favorable. Healing was, however, always more rapid following stasis with small infecting doses, whereas with large doses the reverse happened. In tuberculosis no effect was obtained. White swelling of the knee joint developed equally in the stasis and control legs, and generalization of the disease from the local focus was the same.

Throughout this study the right ear was used as the test ear. All inoculations of tubercle bacilli were given intracutaneously, in 0.1 cc. of sterile 0.9 per cent salt solution. Usually two or three intracutaneous injections were made into the dorsum of the auricle. The experiments are recorded in about the order as performed. Earlier experiments were for the purpose of orientation. In experiment 1a there were 8 rabbits which were divided into four groups of two each, and each of the four groups were inoculated with a different strain of tubercle bacilli—*Human*, an avirulent human tubercle bacillus, *Gluckson* a virulent human tubercle bacillus, *Bovine D* a slightly virulent bovine tubercle bacillus and *Bov. Vir.* a virulent bovine tubercle bacillus—and each rabbit of the two in the individual groups received intracutaneous inoculations of different amounts of the bacilli, one receiving 0.1, 0.001 and 0.000,01 mgm. intracutaneously in three different places in the dorsum of both auricles, and the other receiving 0.001, 0.000,01 and 0.000,000,1 mgm. in three separate places in both auricles. A small constricting rubber band, about one-half inch in diameter, was applied to the base of the right auricle while the left remained the control. The band was at first applied 8 to 10 hours daily and, finally, as the base of the auricle became indurated, continually, being removed probably once weekly or sufficiently long to permit the slight edema to subside, so that readings could be more easily made. All readings were, however, made in two ways, by inspection and palpation, to obviate, as far as possible, errors which might result were inspection alone used.

The rabbits (1 to 4) given 0.1 cc. of *Human* and *Gluckson* bacilli, in amounts of 0.000,000,1 to 0.1 mgm., developed no local infection within an observation period of two months, while those (rabbits 5 and 6) receiving the moderately virulent *Bov. D.* were also negative except from the 0.1 mgm. dose, which produced a small lesion. The lesion in the nonconstricted ear seemed to develop more rapidly than that in the constricted ear. The two rabbits receiving the virulent *Bov. Vir.* developed distinct lesions from doses of 0.001 and 0.1 mgm., as follows:

Experiment 1a:[2] In rabbit 7 the 0.1 mgm. lesion in the normal auricle was larger, both in area and depth, from the seventeenth to the seventy-ninth day than in the constricted auricle, after which all differences were obliterated because of ulceration which occurred in both ears on the thirty-fifth day. The 0.001 mgm. lesions in this rabbit developed earlier and were slightly larger in the normal than in the constricted auricle throughout the 79 days of observation, no ulceration having occurred. No lesions resulted in either auricle from the 0.000,01 mgm. inoculations.

In rabbit 8 no lesions developed from the 0.000,01 and 0.000,000,1 mgm. inoculations in either auricle, while that following the 0.001 mgm. inoculation into the normal auricle was only slightly larger than that in the constricted auricle, arising on the twenty-third day and persisting without ulceration through the seventy-ninth day.

When it was realized that the smaller amounts of bacilli would not suffice, experiment 1b was planned. In this 2 rabbits were given larger doses, 10, 1 and 0.1 mgm. in separate sites in both auricles, one (no. 9) receiving the virulent human *Gluckson*, and the other (no. 10) the virulent *Bov. Vir.* All developed lesions.

Experiment 1b: In rabbit 9 the 10 mgm. inoculation sites in both auricles ulcerated early and there was very little difference between the lesions in the two auricles. The 1 mgm. focus in the constricted auricle ruptured before the eighth day while that in the normal auricle did not rupture until the twenty-third day. The latter was larger from the eleventh to the fortieth day. The 0.1 mgm. inoculation into the constricted auricle produced a lesion smaller than in the normal auricle which ruptured on the thirtieth day.

In rabbit 10 the 10 mgm. lesion was larger in the constricted than in the normal auricle. In both, however, ulceration occurred early, thus obscuring the findings. The 1 mgm. lesion in the constricted auricle also ruptured early and was smaller than that in the normal auricle which ruptured on the eleventh day. The 0.1 mgm. lesion was smaller in the constricted auricle and ruptured on the sixteenth day, while that in the normal auricle ruptured on the thirtieth day.

The findings in rabbits 9 and 10 indicate that the tendency to ulceration, especially when larger infecting doses are used, is greater in the congested than in the normal auricle, and that when large doses of virulent bovine bacilli are used there is a tendency for the entire congested auricle to become involved by multiple, small, metastatic tubercles which do not develop after virulent human (bacilli) infection. This experiment left

[2] The data of all experiments that follow are tabulated in the Transactions of the National Tuberculosis Association, nineteenth annual meeting, 1923.

many points uncertain, however, which it was hoped the subsequent larger series of animals would help clear up.

In the following experiment 2 with 12 rabbits, it was planned to repeat in four animals (nos. 11, 12, 13 and 14) the inoculations given animals 9 and 10 of *experiment 1 b*, and, as, a control, to give 4 more rabbits (nos. 15, 16, 17 and 18) the same bacilli in the same doses, but with the bacilli killed by placing the tubes containing the suspension in a boiling water-bath for one hour; in these 8 rabbits the right auricle only was constricted. The remaining 4 rabbits (nos. 19, 29, 21 and 22) were given intracutaneous inoculations of living bacilli into the right auricle, and the same suspension, but heat-killed, into the left auricle, constriction bands being applied to both ears for 8 to 10 hours daily at first, and then continually except during 12 hours before making readings. Three intracutaneous inoculations of 10, 1 and 0.1 mgm. of tubercle bacilli were given into the dorsum of the auricle, transversely placed, in all 12 rabbits.

Experiment 2: In rabbit 11, that received virulent human bacilli, the 10 mgm. lesions were little different in the two auricles, both ulcerating early, while the 1 mgm. lesion was larger in the normal auricle throughout the 41 days of observation, rupture occurring in both cases on the third day after inoculation. The 0.1 mgm. lesion in the constricted auricle was smaller throughout the 41 days of observation. Ulceration occurred on the nineteenth day in the constricted auricle and on the twenty-seventh day in the normal auricle. Healing was advanced in all the lesions on the forty-first day.

In rabbit 12 the 10 mgm. lesions were variable. They ruptured in both auricles on the third day. The 1 mgm. lesion in the normal auricle, which ruptured on the third day, was of about the same size throughout the 41 days of observations as that in the constricted ear, which did not, however, rupture until the twelfth day. The 0.1 mgm. lesion in the normal auricle was definitely larger, and developed earlier than that in the constricted auricle. At the end of the observation period the lesions in the former, as a whole, were larger than in the latter.

In rabbit 13, that received virulent bovine tubercle bacilli, the 10 mgm. lesions ruptured too early to give readings of any value, while the 1 mgm. lesion was distinctly larger in the normal than in the constricted auricle throughout the experiment. The former ruptured on the twelfth day and the latter on the third day. The 0.1 mgm. lesion in the normal auricle was decidedly larger than that in the constricted auricle, and ruptured on the nineteenth day, while the lesion in the constricted auricle ruptured on the twelfth day. At twenty-three days multiple, metastatic tubercles began

to appear in both auricles. On the forty-first day the right auricle appeared worse than the left on account of the multiple tubercles, although the original lesions in this ear were smaller at this time.

In rabbit 14, a duplicate of no. 13, the findings, except for minor details, were the same as in no. 13. On the thirty-third day reading of local lesions had to be discontinued because the auricles were so mutilated by scratching.

In rabbit 15, that received heat-killed virulent human bacilli in both auricles, the 10 mgm. lesion was larger in the normal auricle, rupture occurring here on the twenty-seventh day and on the third day in the constricted auricle. The 1 mgm. lesion was slightly larger in the constricted auricle, but after the twenty-seventh day both were the same size. The 0.1 mgm. lesions in both auricles were not perceptibly different and did not rupture during the experiment.

In rabbit 16, a duplicate of no. 15, the lesions from the same dosage in both auricles did not appreciably differ from each other at any time. The 10 and 1 mgm. lesions ruptured in both ears on the third day, while the 0.1 mgm. lesion in the constricted ear ruptured on the twelfth day and that in the normal ear did not rupture.

In rabbits 17 and 18, that received the heat-killed virulent bovine bacilli, the lesions due to equal inoculations compared very well with each other. There were slight individual variations which, however, proved of no significance. At forty-one days the lesions in rabbit 17 were fairly equal in the two auricles, while in rabbit 18 those in the normal were slightly larger than in the constricted auricle.

In rabbits 19 and 20, in which both auricles were constricted, the right receiving living virulent human bacilli and the left the same bacilli, heat-killed, in amounts of 10, 1, and 0.1 mgm., all lesions in the right auricle were larger throughout the 19 days of the experiment than those in the left auricle. Those due to living bacilli also developed more rapidly and ulcerated earlier than those due to dead bacilli.

In rabbits 21 and 22, duplicates of nos. 19 and 20, except that virulent bovine tubercle bacilli were inoculated, the same local findings as above were noted. On the nineteenth day, however, autopsy revealed enlarged right auricular lymph nodes in rabbit 21, and enlarged auricular and cervical nodes on the side receiving living bacilli in rabbit 22, while there were none on the side with dead bacilli.

In the 12 rabbits of experiment 2 it was interesting that there was a marked tendency to ulceration of the intracutaneous lesions in the constricted, as compared with the nonconstricted auricle; that there seemed to be a retarding influence upon the lesions by the constriction, especially when the smaller doses of bacilli were used; that, after a certain interval

after infection with virulent bovine bacilli and even though retardation was visible in the local lesion, there developed a general metastatic involvement of the auricles, visible in both the constricted and nonconstricted ears which made further comparisons impossible; that the difference between the lesions in the constricted and nonconstricted auricles, seen when living bacilli were used, did not appear when heat-killed bacilli were inoculated, although the tendency to ulceration seemed to be slightly greater in the constricted auricle even with dead bacilli; and that living bacilli, both virulent human and bovine, tended to produce progressive lesions in the rabbit's auricles, when compared to dead bacilli.

In view of the fact that thus far all comparsions of lesions produced by living and dead bacilli were made in opposite auricles, and thus both auricles in the same animal had to be constricted, it was decided to compare the effects of living and dead (heat-killed) bacilli in the same auricle; by using the same doses of bacilli in the opposite auricles as well, a more accurate comparison of the differences between the effects of living and heat-killed bacilli was possible as well as a determination of the effect of constriction of the auricle upon the resulting lesions.

Experiment 3 was thus planned: One rabbit received an intracutaneous inoculation of 0.1 cc. of a suspension of virulent human bacilli (*Gluckson*), containing 0.1 mgm. of bacilli, on one side of the dorsum of the auricle, and a second injection of the suspension, previously killed by placing it in a boiling water bath for an hour, on the other side of the dorsum of the shaved auricle. Two identical inoculations were then given into the other auricle. A second rabbit received in each inoculation site 1 mgm. of bacilli instead of 0.1 mgm., and two others were given 1 and 0.1 mgm., respectively, of virulent bovine bacilli (*Bov. Vir.*), live and heat-killed. Readings were then made at intervals as in previous experiments.

Experiment 3, Part 1: In rabbit 23, given 0.1 mgm. of virulent human bacilli living and dead, in each auricle and with the right auricle constricted, the lesions resulting from the inoculation of the dead bacilli developed about equally and with the same rapidity during the 26 days of the experiment, while the lesions due to the living bacilli in the normal auricle developed more rapidy and to greater size than in the constricted auricle. None of the esions ruptured in this animal.

In rabbit 24, a duplicate of no. 23, except that 1 mgm. of bacilli was inoculated, all of the living bacillus lesions ruptured on the third day, and on the ninth and twelfth days in the constricted and normal auricles, respectively, when produced by dead bacilli. The striking difference between the lesions in the constricted and normal ears that was seen in rabbit 23 was not noted here,

although the lesions in the normal auricle, due to living bacilli, developed more rapidly than in the right auricle. Up to the twelfth day the lesions due to dead bacilli were equal in both auricles, but after this the lesion in the left auricle was slightly larger, although never to the extent seen after living bacilli.

In rabbit 25, that received 0.1 mgm. of virulent bovine bacilli, the lesion due to living bacilli in the normal auricle developed more rapidly and was larger throughout the experiment than that in the constricted auricle while the lesions due to dead bacilli were very little different in the two auricles. Ulceration occurred in both lesions due to living bacilli on the ninth day. The lesions due to dead bacilli did not rupture. Multiple metastatic lesions appeared in both auricles on the twenty-sixth day; and the original lesion in the normal auricle, due to living bacilli, still appeared larger than that in the constricted auricle while both lesions due to dead bacilli had healed.

In rabbit 26, that received 1 mgm. of virulent bovine bacilli, the lesion due to living bacilli in the constricted auricle ruptured on the third day and in the normal auricle on the ninth day, while that due to dead bacilli ruptured on the fifth day in the constricted and the ninth day in the normal auricle. The lesion due to living bacilli in the normal auricle developed more rapidly and reached a greater size than in the constricted auricle. Those due to dead bacilli were of equal size until the ninth day, after which that in the normal auricle was slightly larger than in the constricted auricle, but never to the extent seen after living bacilli. Multiple lesions appeared in both auricles on the twenty-sixth day. On the fifty-sixth day the original lesions, due to living bacilli, in the normal auricle were still larger than in the constricted auricle.

The findings recorded in the above part of experiment 3 would indicate that constriction of the rabbit's auricle has a definite retarding influence on the local, intracutaneous, tuberculous lesions developing after inoculation of virulent human and bovine bacilli, compared with the lesions due to the same inoculations (1 and 0.1 mgm.) in nonconstricted normal auricles, while the lesions resulting from inoculations of dead bacilli are not appreciably influenced by the constriction, except, possibly, that the previously noted tendency to ulceration is slightly greater in the congested auricle.

Since in experiment 2 (rabbits 21 and 22) constriction was applied to both ears when the effects of dead and living bacilli were compared in opposite ears of the same rabbit, two other rabbits, nos. 27 and 28, were included in this experiment. In these living bacilli were inoculated into

one auricle (10, 1, and 0.1 mgm.) and the same suspensions, heat-killed, into the other auricle, but neither was constricted. One rabbit, no. 27, was given inoculations of virulent human bacilli (*Gluckson*) and the other, no. 28 virulent bovine bacilli (*Bov. Vir.*) with the following results:

Experiment 3, Part 2: In rabbit 27, given virulent human bacilli, the lesion in the left auricle proved to be nonprogressive. After the larger doses (10 mgm.) rupture occurred on the fifth day, and after 1.0 mgm. on the twelfth day, while after 0.1 mgm. rupture did not take place. In the right auricle the living bacilli produced lesions of a more progressive nature, which ruptured earlier than those resulting from dead bacilli and attained a greater size during the experiment. Rabbit 28, in which virulent bovine bacilli were used, gave about the same findings as those in rabbit 27, except that the lesions in the right auricle, due to the living bacilli, were extensive and multiple on the thirty-fourth day, while those in the left were retrogressing and healing at this time. The right auricular lymph nodes were also definitely enlarged at this time.

The second part of experiment 3 (rabbits 27 and 28), in which constriction was not applied to the auricles after infection, bears out the findings with rabbits 19, 20, 21 and 22, in which constriction was thus applied. While the living bacilli produced progressive lesions, less so in the case of virulent human than with virulent bovine bacilli, the dead (heat-killed) bacilli produced nonprogressive lesions. The wide variation in reaction of individual rabbits to the same dose of bacilli was again seen in these animals, although a complication existed in the marked tendency for the lesions to ulcerate, especially those from larger doses or when congestion existed.

The foregoing experiments were not entirely satisfactory. It was felt, first, that a more suitable dosage of bacilli could be used, since the previous amounts were seemingly excessive, and favorable to early ulceration of lesions which then lessened the value of the readings. In the second place, a more extended period of observation, which would be possible with better-graded doses, would have its advantages when dealing with tuberculosis that is naturally complicated by factors of virulence, lesion production, tissue injury and progression and growth. A larger series of animals planned and observed on the basis of experience gained from the previous experiments, would, no doubt, obviate possible error, both in observation and interpretation.

Experiment 4: Included 12 rabbits, given intracutaneous inoculations of 0.1 cc. of sterile salt solution, containing 0.1, 0.01 and 0.001 mgm. of living tubercle bacilli, in the dorsum of each auricle. Six received virulent human (*Gluckson*) and the other 6 virulent bovine bacilli (*Bov. Vir.*). The right auricle was constricted with a small rubber band at the base of the ear, applied daily for about 8 to 12 hours and finally continuously and only removed for 12 hours before making readings. The purpose was to obtain a mild congestion, with at times a slight edema, of the constricted auricle throughout the study. Postmortem examination of most of the animals was made on the ninty-third day after infection and detailed observations of the local lesions were usually carried up to the forty-third day. The animals given the human bacilli usually were easily observed even after this time, but those receiving the bovine bacilli developed complications which made accurate observation more difficult. The summarized results of the experiment were as follows:

The findings corroborated those previously noted in the smaller series. The most striking difference between the lesions resulting from the human and bovine bacilli in the constricted and nonconstricted auricles was the earlier rupture and discharge of those in the former; when, however, rupture did not occur, most of those in the constricted auricles were smaller than those in the nonconstricted auricles, although in an occasional animal or occasional lesion this difference was not appreciable. When, however, the stage of general involvement of the ear became manifest, as was usual after bovine infection, all differences previously discernible became overshadowed by the massive involvement. In the majority of animals, when the lymph nodes (auricular, cervical and axillary) draining the ears became involved, there was no appreciable difference between the two sides. In some rabbits, however, the tributary nodes of the congested auricle were distinctly more involved than those of the noncongested auricle. The reason for this difference was not ascertained, although the continual injury due to the rubber band at the base of the auricle may have been instrumental in causing this difference; the inconstancy of the finding made this seem likely.

DISCUSSION

When it is considered that the difference between the carbon dioxide content of the constricted and that of the nonconstricted auricle is not great, and from the viewpoint of the differences attainable in *in vitro* studies, the effects noted in this study are rather more striking than might be

expected offhand. The constricted auricle had only 10 to 20 per cent more plasma bicarbonate than the normal auricle. Realizing this, it is easily appreciated that only a few hours' constriction daily, as practised by Baumgarten in his experiments (1906), could hardly be expected to have an appreciable influence on the tuberculosis, and especially in the form studied by him. If such studies as these are to reveal any effect at all, it is also presumable that, after the stage of massive involvement or dissemination, little can be expected of an agent unless in a form which is at present inconceivable. It must be remembered, too, that experiments of the type recorded are complicated by innumerable factors. One in particular that cannot be ignored is the effect of the congestion and edema on the cellular protective mechanism. In the combat of the body against tuberculosis the cellular mechanism is so well recognized that it hardly needs more than passing mention. The numerous factors which, however, may beneficially or detrimentally influence this protective mechanism are still in the course of analysis and study; and, since there is no direct contrary evidence, it is fair to assume that the congestion and edema of the type used can only have a detrimental influence or no influence at all on it. It is difficult to see how it can influence the cells beneficially. Since, however, the auricle constrictions had a retarding influence on the development of intracutaneous lesions in the majority of the cases, it may be assumed that at least one of the important factors in producing this effect was the small but definite increase in the plasma bicarbonate, which can thus be correlated with the previously reported *in vitro* studies. Whether such information as this can be applied practically depends entirely upon the relations which exist between the tubercle bacillus as it occurs in the body and the body-fluid supply to the bacillus, concerning which we unfortunately have no available scientific data at present. Encouraging, however, from another viewpoint are the chemotherapeutic possibilities derived from this study.

That these experiments may not be misunderstood, it may be well to point out that drastic procedures, such as used in experiments of this nature, are hardly applicable to human therapy for two important reasons; first, in that considerable tissue injury to the constricted auricle occurred which was uncontrollable; and, second, in that when dealing with virulent bovine infection generalization of the disease was not prevented. In a few of the animals the destructive ear condition, due to the prolonged constriction, continued in spite of removal of the constricting band, and

sloughing of the auricle resulted. These experiments must, therefore be construed as of experimental and academic value only.[3]

SUMMARY

The carbon dioxide content of the blood plasma obtained from a congested auricle, produced by applying mild constriction of rabbits' ears, was about 10 to 20 per cent more in terms of bicarbonate than that from normal auricles, and in exceptional cases as much as 50 per cent more. The blood from the normal auricle contained about the same amount of plasma bicarbonate as venous (jugular) blood, although frequently the value lay between the venous and arterial plasma figures. The blood corpuscle-plasma relation was only slightly changed in the congested and edematous auricle, the corpuscles being slightly decreased.

Tubercles, resulting from the intracutaneous inoculation of graded amounts of virulent human and bovine tubercle bacilli, tended to ulcerate and discharge their contents earlier in the congested than in the noncongested auricle of the same rabbit.

The development of local tubercles is retarded by prolonged constriction (at first eight hours daily, and finally continuously) of the base of the auricle, with its resultant continuous mild congestion and edema. This effect is not discernible when heat-killed bacilli are used.

Prolonged mild constriction of the auricle, with its resultant mild congestion, has no appreciable influence on the development of multiple metastatic lesions resulting from infection with virulent bovine bacilli. With virulent human bacilli such lesions do not develop after the dosage and time interval used in this study. Prolonged mild constriction of the auricle also has no appreciable influence on the development of tuberculosis in the regional lymph nodes of the ear after infection with virulent human or bovine bacilli.

Dr. Harold Freed, to whom we are duly grateful, aided materially in the chemical phases of this study.

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[3] It is interesting that Petersen and Levinson have obtained similar results in liver tuberculosis of rabbits, by blocking the pulmonary capillaries with oil, work that was reported at the 1923 meeting of the American Medical Association at San Francisco.

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FIG. 1. EARS OF RABBIT 7, SEVEN WEEKS AFTER INTRACUTANEOUS INOCULATION OF 0.1, 0.001 AND 0.000,01 MGM. OF VIRULENT BOVINE TUBERCLE BACILLI INTO EACH AURICLE
The right auricle was constricted at the base

FIG. 2. EARS OF RABBIT 11, TWO WEEKS AFTER INTRACUTANEOUS INOCULATION OF 10.0, 1.0 AND 0.1 MGM. OF VIRULENT HUMAN TUBERCLE BACILLI, SHOWING TENDENCY OF LESIONS IN CONSTRICTED (RIGHT) AURICLE TO RUPTURE AS COMPARED TO NONCONSTRICTED (NORMAL, LEFT) AURICLE

FIG. 3. EARS OF RABBIT 23, TWO WEEKS AFTER INTRACUTANEOUS INOCULATION OF 0.1 MGM. OF LIVING (*L*) AND HEAT-KILLED (*D*) VIRULENT HUMAN TUBERCLE BACILLI
Right auricle constricted. Note resemblance of lesions due to dead bacilli and difference between those due to living bacilli in the two auricles.

FIG. 4. EARS OF RABBITS 27, ONE WEEK AFTER INTRACUTANEOUS INOCULATION OF LIVING (RIGHT AURICLE) AND HEAT-KILLED (LEFT AURICLE) VIRULENT HUMAN TUBERCLE BACILLI
No constriction of auricles

FIG. 5. EARS OF RABBIT 35, THREE WEEKS AFTER INTRACUTANEOUS INOCULATION OF 0.1, 0.01, AND 0.001 MGM. OF VIRULENT BOVINE TUBERCLE BACILLI
Right auricle constricted

FIG. 6. EARS OF RABBIT 35, FIVE WEEKS AFTER INFECTION

FIG. 7. EARS OF RABBIT 36, FIVE WEEKS AFTER INTRACUTANEOUS INOCULATION OF 0.1, 0.01, AND 0.001 MGM. OF VIRULENT BOVINE TUBERCLE BACILLI
Right auricle constricted

FIG. 8. EARS OF RABBIT 40, SEVEN WEEKS AFTER INTRACUTANEOUS INOCULATION OF 0.1, 0.01 AND 0.001 MGM. OF VIRULENT BOVINE TUBERCLE BACILLI
Right auricle constricted. Note generalization of tuberculosis in both auricles, making further comparison difficult.

Fig. 1

Fig. 5

Fig. 2

Fig. 6

Fig. 3

Fig. 7

Fig. 4

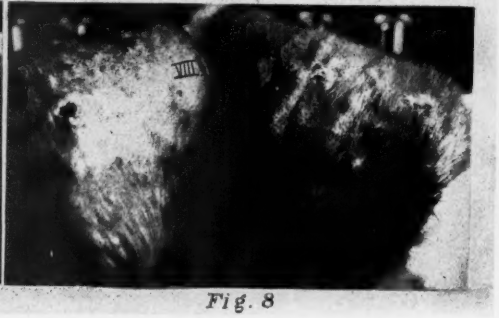

Fig. 8

THE EFFECT OF INJECTIONS OF FOREIGN PROTEIN ON EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS[1]

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Denver

Nonspecific therapy may be said to have originated with the earliest medical treatment. The literature on this subject is extensive and can only be referred to in passing. The enthusiasm accompanying the use of Schaefer's phylacogens, Römer's auto-serotherapy and other nonspecific biological products has usually been short-lived; yet Jobling and Petersen believed that "The very fact that it did do certain things at times should have led to a study of why such favorable changes were brought about." (1) Matthes in 1895 believed he had demonstrated that an albumose produced the same reaction that obtained with tuberculin and explained the fever as produced by protein-split products. Some enthusiasts have advocated milk injections for numerous conditions, including tuberculosis, especially of the eye (2) (3). Cow's milk boiled from five to ten minutes or some other proprietary preparation from milk, such as *caseosan*, *ophthalmosan*, *aolan*, *Yatrencasein*, etc. have been used (4).

It was admitted that the treatment could be only symptomatic, if it had any action at all upon the diseased processes. A satisfactory explanation, likewise, of any action which has been seen, whether due to a change of ferment balance (defensive ferments), allergy, or purely chemical irritation, is lacking, although some authors (4) liken the action to that of tuberculin. Selter (5), in studying the reactions to *caseosan*, peptone, tuberculin and bacterial toxins, is inclined to view the tuberculin reaction as consisting of two factors, a nonspecific factor, naturally existing, to bacterial and other proteins, and a specific, developed factor of tuberculous nature. In pulmonary tuberculosis Suess (6) has utilized milk injections for therapeutic purposes. In a guinea pig he found that milk acted differently from tuberculin in not being lethal for a tuberculous guinea pig. In man he found an analogy

[1] From the Research Department, National Jewish Hospital for Consumptives, Denver, Colorado.

between the reaction to tuberculin and milk only in the ability to produce fever. There was, however, during tuberculin treatment not only a decreasing hypersensitiveness to tuberculin but also to nonspecific substances, while in certain cases the milk increased tuberculin hypersensitiveness. The milk-treated cases, according to him, were favorably influenced, but it seems that they were also given tuberculin, thus introducing a complicating factor.

In reviewing the literature on nonspecific protein therapy in experimental tuberculosis, it was noted that in 1919 Krause and Willis (9) had used egg-white intraperitoneally and found that control animals resisted infection better than protein-treated animals. Native egg-white was given in amounts of 0.5 to 2 cc. each for a total of 70 injections over a period of three months before infection, in experiment 1. The animals were infected subcutaneously with one drop of a virulent tubercle bacillus suspension (1 bacillus to every four or five oil-immersion fields) and the animals were examined for tuberculosis sixty days later. In a second experiment they used a slightly virulent tubercle bacillus (0.25 cc. of a heavy emulsion) and gave egg-white (0.5 cc. increased to a daily maximum of 2 cc. five or six times weekly, until 58 injections had been given, subsequent to (thirty-eight days after) infection). The animals were examined 117 days after infection and practically no difference was noted between the treated guinea pigs and the controls. In a third experiment repeated protein (egg-white) intoxication ("chronic anaphylaxis") following upon infection with a comparatively avirulent tubercle bacillus also did not appreciably alter the guinea pigs' resistance to tuberculosis.

In view of the favorable reports in the literature on nonspecific protein therapy in ocular tuberculosis and the suggestions of beneficial effects in pulmonary tuberculosis, it was thought advisable to test out its effect in experimental animals, using, however, accurately graded doses of bacilli. In reviewing the literature it seems that milk and egg white have received the most enthusiastic support clinically and are considered less harmful than other proteins that have been used. Fortunately, experimental tuberculosis in the guinea pig to graded infecting doses of bacilli had been elaborately studied by Krause (7) and Rensch and Moore (8), so that every appreciable influence of a therapeutic agent, tested in a large enough series of animals given graded subcutaneous injections of tubercle bacilli, should give an indication as to whether there is any effect upon the tuberculosis *per se*.

Before initiating the experiments it was realized that the foreign proteins, milk and egg-white, could only be administered to the guinea pigs in repeated daily doses of sufficient size to avoid the development of anaphylaxis to which these animals are highly susceptible. To avoid giving overwhelming doses of living bacteria normally found in market milk, the milk was sterilized by boiling for at least three to five minutes. The egg-white used was obtained from fresh eggs by washing them well with soap and water and then immersing them in 50 per cent alcohol for ten minutes, opening the shell and separating the white into a sterile container with sterile precautions. The egg-white was then injected without heating or the addition of any antiseptic. In all the experiments to be reported a virulent human tubercle bacillus ("Gluckson") was used for infection by injecting the suspension in physiological salt solution, subcutaneously, into the left groin of guinea pigs, in three different amounts of 0.1, 0.0001 and 0.000,000,1 mgm. The experiments were conducted in three distinct series, each consisting of about 24 male guinea pigs weighing about one pound, of which 6 served as controls and the remaining 18 animals as tests. Repeated injections of foreign proteins in the form of egg-white and milk were given for six weeks. In series 1 subcutaneous injections of egg-white in 3 cc. amounts were given twice daily, and intramuscular injections of sterile milk on alternate days in 1 to 1.5 cc. amounts. Six days after the initiation of the foreign protein injections the animals were given subcutaneous injections of the suspensions of tubercle bacilli. The animals were examined five weeks thereafter. Series 2 differed from series 1 only in that the foreign protein (milk and egg-white) injections were initiated on the day of tuberculous infection, the animals being examined six weeks after infection. In series 3 the foreign protein injections were begun six days after initiation of tuberculous infection. The animals were examined six weeks after infection. The results of the postmortem findings in these three series of guinea pigs five and six weeks after infection are recorded in table 1.

The milk injections caused a severe inflammatory reaction at the site of injection at times which, however, subsided in a few days. The egg-white injections were absorbed readily for the first week, but later the absorption seemed to be so greatly impaired that injections had to be discontinued entirely at the end of the third week. In a few of the animals encysted sterile milk abscesses developed. The temperature

TABLE 1

The effect of egg-white and milk injections initiated before and after infection upon experimental tuberculosis in the guinea pig

SERIES	ANIMALS	NUMBER	INFECTING DOSE IN MILLIGRAMS OF VIRULENT HUMAN TUBERCLE BACILLI "GLUCKSON"		
			0.000,000,1	0.000,1	0.1
1* Foreign protein injections initiated 6 days prior to infection	Controls	1	++†	++++	++++
		2	+	++	++++
	Treated	3	++	+++	++++
		4	+	+++	++++
		5	+	+	++++
		6	+		
		7	+		
		8	+		
2 Foreign protein injections initiated coincident with infection	Controls	1	+++	+++	++++
		2	++	+++	++++
		3	++	+++	++++
		4	++		
	Treated	5	++	+++	+++
		6	++	++	+++
		7	+	+++	+§
		8	+‡	+++	+§
		9	+‡	+++	
		10		+++	
3 Foreign protein injections initiated 6 days after infection		11	++	++++	++++
		12	++	+++	+++
		13	++	+++	++△
		14	+	++	++

* The animals in series 1 were examined five weeks after infection and in series 2 and 3 six weeks after infection. The controls for series 2 also serve as controls for series 3, both series being infected on the same day.

† The tuberculous involvement in the guinea pigs is graded from 0 to ++++ as follows:
O = no visible macroscopic tuberculosis.

\+ = Distinctly enlarged local and slightly enlarged retroperitoneal lymph nodes.

++ = Enlarged local and retroperitoneal nodes and slight involvement of spleen.

+++ = Enlarged local and retroperitoneal nodes, and spleen markedly involved, the peritracheal nodes enlarged and the lungs slightly involved.

++++ = Massive involvement of all nodes, spleen, lungs and liver.

‡ Died in 3 weeks.

§ Died in 2 weeks.

△ Died in 4 weeks.

of the guinea pigs was taken for three days before injection of the foreign proteins and during the first week following injections. There occurred a slight rise in temperature from 1° to 2.5° which, however, did not differ greatly from that seen in the noninjected guinea pigs. Mild emaciation occurred in almost all the guinea pigs given the foreign protein injections, although the appetite was not impaired by the injections.

An examination of the experimental data in table 1 indicates that large injections of foreign protein in the form of sterilized milk and native egg-white, administered subcutaneously and intramuscularly to tuberculous guinea pigs for four weeks or more, has no appreciable effect upon the course of the tuberculosis in these animals, as determined by the anatomic tuberculous involvement after graded infecting doses. The relations between tuberculous organ involvement and lymph node involvement were also noted, but there was found no regular or consistent relationship which could be considered of any significance.

These experiments entirely corroborate the previous studies by Krause and Willis, although the technique of their performance differed in detail.

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CONSTIPATION IN TUBERCULOSIS[1]

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Constipation occurs as a troublesome and unpleasant condition, associated with pulmonary tuberculosis quite as frequently as with other diseases. The extended period of bed rest, which is of primary importance in the treatment of tuberculosis, is conducive to an increased incidence of constipation in patients with tuberculosis.

The following observations were made by the staff of the Koch Hospital for Tuberculosis of the City of St. Louis, as part of an effort to extend the study of the gastrointestinal accompaniments of pulmonary tuberculosis. The observation is unusual, as a mass observation of all cases in the institution during the same period.

These observations demonstrate the results which may be obtained by a simple regimen applied as a hospital measure. The results illustrate the help which may be readily obtained in sanatoria and hospitals, and demonstrate the very great comfort, if not positive benefit, which may be given the tuberculous patient with correction of the constipation by means of other agents than laxatives.

Constipation is considered as a condition of delayed, inadequate and infrequent defecation. Among the many causes which have been mentioned are the inspissation of the feces, the lack of adequate fluid intake, errors in diet, sedentary habits, visceroptosis, kinking of the colon at the flexures and by membranes, hypertonicity and hypotonicity of the colon musculature, fissures and fistula in ano, anomaly of the rectal folds, hypertonic sphincters, local colonic redundancies, spasticities of the rectosigmoid apparatus, and pathological strictures and tumors. In the group of cases considered in this paper constipation was coincident with bed rest in 27 cases, as shown by the indicated division in table 2. Whatever the causes operating to produce constipation, a proper colon content is considered essential to correction by other measures, if such then become necessary. The corrective regimen as

[1] From the Koch Hospital for Tuberculosis of the City of St. Louis.

used was based upon the dictum that the constipated stool is the greatest stimulus to constipation. The measures were directed to secure for the colon a content which would remain soft and plastic and permit normal peristaltic colonic movements. Bran was used as a breakfast food and in a very palatable bread unusually well prepared by the hospital baker. Patients enjoyed this bread and did not tire of it. Mineral oil was administered almost routinely as one tablespoonful after each meal. Agar was used in only a few cases.

TABLE 1

Frequency of laxative administration

	CASES
Daily	9
Once in 2 or 3 days	12
Once in 3 or 4 days	10
Once in 4 or 5 days	7
Once in 5 or 6 days	10
Occasionally	10

TABLE 2

Duration of constipation

	CASES
20 to 25 years or more	4
15 to 20 years or more	2
10 to 15 years or more	3
5 to 10 years or more	2
4 to 5 years or more	5
3 to 4 years or more	3
2 to 3 years or more	5
1 to 2 years or more	7
	—
	31
	—
½ to 1 year or more	8
1/12 to ½ year or more	19
	—
	27

Among the 200 cases in the hospital 58 had been receiving laxatives for chronic constipation. Of these, 23 cases received bran and bran bread only, and 35 received, in addition, one tablespoonful of mineral oil two or three times daily after meals.

Following the regimen it became necessary to give laxatives in only 13 of the cases. A small number of cases became slightly diarrheic

TABLE 3

Frequency of bowel movements

	BEFORE REGIMEN		AFTER REGIMEN	
	Cases	Per cent	Cases	Per cent
With purgative only	5	8		
Once in 4 or 5 days	4	7.5		
Once in 3 or 4 days	8	14		
Once in 2 or 3 days	12	20.5		
Once in 1 or 2 days	13	22.4	6*	10.5
Daily inadequate	16	27.6	6†	10.5
Daily adequate			10	17.5
1 to 2 stools daily			31	53
2 to 3 stools daily			3	5.5
3 to 4 stools daily			2	3

* Six cases were entirely uncorrected.

† Six cases were partially corrected.

TABLE 4

Summary of weight status

	2 MONTHS PRIOR TO REGIMEN							2 MONTHS OF REGIMEN					
	Number of cases			Total of group in pounds		Average for group in pounds		Number of cases.		Total of group in pounds		Average for group in pounds	
	Total	Gaining	Losing	+	−	+	−	Gaining	Losing	+	−	+	−
Constipation corrected													
Symptoms relieved													
Tuberculosis													
Progressive	6	5	1	21		3½		1	5		6½		1 1/12
Retrogressive	12	7	3	15½		1¼		11	1	38½		3¼	
Stationary	10	5	4	4		4/5		6	2	15½		1½	
Symptoms improved													
Tuberculosis													
Progressive	3		1		5		1⅔		2		14		4⅔
Retrogressive	2	2		5		2½		2		6½		3¼	
Stationary	6	5	1	12½		2 1/12		6		30		5	
Constipation uncorrected	3	2		16		5⅓			2		9		3

with these additions to the diet, and it was necessary to reduce the amounts for them. Constipation was relieved irrespective of the duration shown in table 2.

Sixteen cases were receiving some sedative preparation for their cough, and of these only 4 were unrelieved of their constipation and in the latter there was no reason to consider the sedative as a cause for failure.

Forty-two cases were followed for their weight status during the two months preceding and the two months following the introduction of the regimen. Among 22 patients in whom the tuberculosis was stationary or retrogressive, and whose constipation was corrected with relief of symptoms and improvement of appetite, only 3 lost weight the two months of the regimen as against 7 the two months preceding. The average gain in weight for two months of the constipation treatment was 2.45 lbs. as against 0.9 lb. for the two months preceding.

For 8 similar cases whose constipation was corrected, but who were only partially relieved of their discomforts, the average gain in weight was, nevertheless, greater the two months following the regimen, being $4\frac{1}{2}$ lbs. as against $2\frac{1}{3}$ lbs. for the two months preceding.

All cases of progressive tuberculosis showed an increased loss of weight in spite of the relief gained otherwise.

SUMMARY AND DISCUSSION

Of 58 cases of pulmonary tuberculosis, having constipation as a troublesome symptom and receiving laxatives for its correction, 49 were corrected by inclusion in the diet of adequate quantities of bran associated in some cases with the administration of mineral oil.

Thirty-five cases were relieved of abdominal discomfort and were improved in appetite. The weight balances of 28 of these were tabulated. Of these, 22 in whom the tuberculosis was stationary or retrogressive showed an accelerated gain in weight and the other 6 in whom the tuberculosis was progressive changed from a gain to a loss in weight.

Fourteen cases were improved either by relief of abdominal discomfort or by improvement of appetite. The weight balances of 11 of these were tabulated. Eight cases of stationary or retrogressive tuberculosis showed an accelerated gain in weight. Cases with progressive tuberculosis showed an accelerated loss in weight.

No attempt is made here to treat specifically of the varied problems of constipation. These observations are presented as an unique mass demonstration of the prompt correction of a large proportion of cases of constipation by very simple routine measures, with resulting great benefits to the patients, benefits which in pulmonary tuberculosis have

a direct influence upon the disease. It is notable that bran alone was very effectual, but better results were obtained by the associated use of mineral oil.

CONCLUSIONS

1. Constipation in the patient with pulmonary tuberculosis unfavorably influences the course of the disease.

2. Relief of constipation in tuberculous patients results in the relief of abdominal discomforts and improvement of appetite, and is favorable to a gain in weight.

3. Constipation in the greater proportion of tuberculous patients may be readily relieved by a simple hygienic and dietetic regimen, directed to provide an adequate soft content to the colon.

4. Direct attention and care should be given to tuberculous patients subjected to bed rest that the resulting constipation may be promptly considered and corrected.

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